ARCHIVES OF SURGERY

VOLUME 42 APRIL 1941 NUMBER 4

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CHANGES IN THE LIVER ASSOCIATED WITH HYPERTHYROIDISM

WITH A STUDY OF PLASMA PROTHROMBIN LEVELS IN THE IMMEDIATE POSTOPERATIVE PERIOD

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During the past nine years considerable interest has been aroused concerning the state of the liver in patients with hyperthyroidism, and excellent studies of the morphologic and physiologic changes in this organ associated with increased activity of the thyroid gland have been reported. Despite the evidence of such a possible relation, however, many patients with hyperthyroidism are treated without regard for hepatic function so far as the type of diet is concerned. Attention has been focused on a high caloric intake, with disregard of the carbohydrate-fat ratio and the vitamin requirements.

ANATOMIC CHANGES

Cameron and Karunaratne[1] have summarized the development of knowledge concerning the hepatic changes accompanying hyperthyroidism, and Boyce and McFetridge[2] have reviewed the significant clinical and pathologic contributions which have been made to this subject in recent years.

In 1932, Weller,[3] in studying the morphologic changes in the livers of 48 patients who died with hyperthyroidism, compared the data with those on a group of controls who were carefully selected to rule out

This study was carried out under a grant from the John and Mary R. Markle Foundation.

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1. Cameron, G. R., and Karunaratne, W. A. E.: Liver Changes in Exophthalmic Goiter, J. Path. & Bact. **41**:267 (Sept.) 1935.

2. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Test: II. Thyroid Disease, Arch. Surg. **37**:427 (Sept.) 1938.

3. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543 (Nov.) 1933.

diseases known to cause pathologic changes in this organ. He found that chronic patchy parenchymatous interlobular hepatitis was the characteristic lesion and noted it to be present to a marked degree in 26 of the 48 subjects and to be slight in 16. In only 6 were no hepatic lesions present. In contrast, in the control series of 48, only 1 liver showed marked interlobular hepatitis; 14 presented slight changes, and 33 were normal.

Beaver and Pemberton [4] in the same year studied 107 autopsies on patients with hyperthyroidism and described in detail three types of pathologic changes in the liver in these cases. These were represented (1) by acute degenerative hepatic lesions varying from fatty degeneration to acute parenchymatous necrosis, the distribution of which was in some instances central and in others focal; (2) by chronic atrophy in which reduction in the weight of the liver with diminution in the size of the hepatic cells were the chief observations, and (3) by chronic cirrhosis similar to the change described by Weller. Beaver and Pemberton were able to correlate the acute degenerative hepatic lesions with those present in cases of severe clinical hyperthyroidism and found that in 57 per cent of the entire series hepatic necrosis was a feature. In all but 2 patients with a basal metabolic rate above + 60 per cent acute hepatic lesions were present. They noted further that the acute changes were usually found in patients whose hyperthyroidism was of short duration. Finally, all patients who died in crisis showed acute degenerative lesions in the liver. Chronic cirrhotic changes and simple atrophy were found in the livers of patients with long-standing hyperthyroidism and patients in the older age group. In their series of 107 cases, jaundice was a significant feature clinically in 21.5 per cent and could be explained on the basis of the hepatic lesion in all but 4 cases.

Shaffer [5] has recently reviewed the subject, adding a carefully studied series of 24 autopsies on patients with hyperthyroidism, and has confirmed the findings of Weller and of Beaver and Pemberton. He added that the changes in the liver apparently are not due to deficiencies of vitamins B and C.

In the surgical service of the New York Hospital 680 patients with hyperthyroidism have been subjected to some form of operation on the thyroid gland in the past eight years, and 16 of these have died. Of this group of 16, 8 died in typical thyroid crisis. Autopsies were performed on 6 of the 16. The pathologic changes in the liver in this group of 6 patients resembled those described by Beaver and Pemberton.

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4. Beaver, D. C., and Pemberton, J. deJ.: Pathological Anatomy of Liver in Exophthalmic Goiter, Ann. Int. Med. **7**:687 (Dec.) 1933.

5. Shaffer, J. M.: Disease of the Liver in Hyperthyroidism, Arch. Path. **29**:20 (Jan.) 1940.

In the accompanying table are listed the significant clinical and pathologic data in the 6 cases. The weight of each liver was within normal limits. Grossly, the picture varied from that of a liver of normal color and consistency to that of finely nodular cirrhosis with increased consistency. All of the livers exhibited moderate to marked amounts of yellow mottling. Microscopically, the three outstanding observations were (1) large droplets of fat diffusely distributed in the parenchymatous cells; (2) central necrosis of the hepatic cords as evidenced by karyolytic and pyknotic nuclei, eosinophilic, homogeneous cytoplasm and actual loss of cells, with marked infiltration of the necrotic areas by polymorphonuclear leukocytes and red blood cells, and (3) a moderate to marked degree of connective tissue proliferation in the portal spaces, with accumulation of lymphocytes. In case 5 there was a typical picture of moderate nodular cirrhosis.

Changes in the Liver in Cases of Fatal Hyperthyroidism

		Gross and Microscopic Condition of Liver				
Case	Jaundice	Weight, Gm.	Atrophy	Fatty Degeneration	Focal or Central Necrosis	Chronic Cirrhosis
1	0	1,700	0	++	0	0
2	0	1,650	0	++	++	0
3	0	1,745	0	++	+++	++
4	+	850	0	+++	++++	++
5	++	1,450	0	+++	0	+++
6	0	1,600	+	++	0	0

+, slight; ++, slight to moderate; +++, moderate to severe; ++++, severe.

REPORT OF CASES

CASE 1.—The patient was a 54 year old white man with a large, mildly toxic nodular goiter. He was operated on, under avertin with amylene hydrate and nitrogen monoxide and oxygen anesthesia, and showed no marked postoperative reaction. He died one month later of bronchopneumonia, and at autopsy the liver showed only a moderate degree of fatty degeneration.

CASE 2.—A 35 year old white woman was admitted to the hospital with a toxic diffuse goiter and cardiac damage secondary to the hyperthyroidism. Her symptoms were of one year's duration, and on admission her basal metabolic rate was + 65 per cent. After an adequate preoperative preparation of four weeks' duration she was subjected to a subtotal thyroidectomy, under avertin with amylene hydrate and ether anesthesia. At the time of closure of the incision and without previous untoward reaction the patient's heart suddenly ceased beating, while respirations continued for several seconds. Attempts at resuscitation were of no avail. Clinically, the impression was that ventricular fibrillation was the cause of death. At autopsy the heart was essentially normal grossly and showed only small areas of subepicardial fragmentation of the myocardial fibers microscopically. The liver exhibited a moderate degree of fatty degeneration and acute focal necrosis.

CASE 3.—A 45 year old white woman had a toxic nodular goiter and severe congestive heart failure of two years' duration, secondary to chronic endocarditis

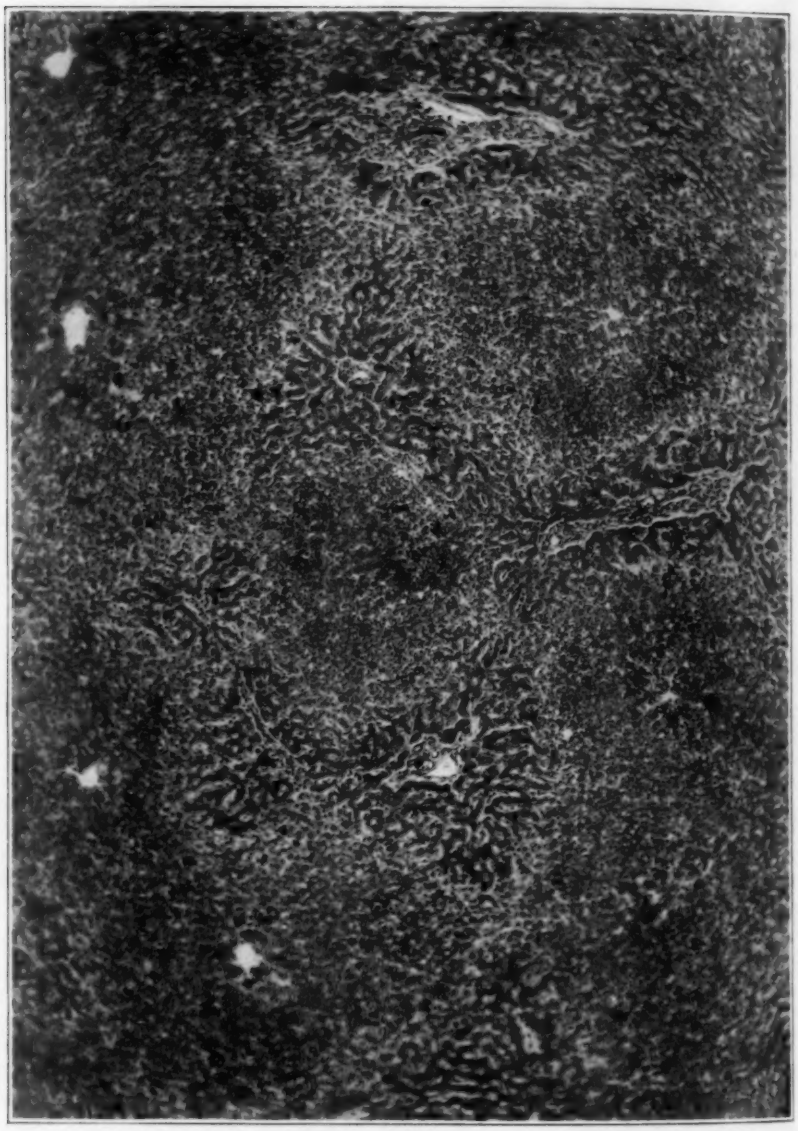

Fig. 1.—Photomicrograph of the liver in case 4, showing advanced necrosis in the central three fourths of each lobule. × 90.

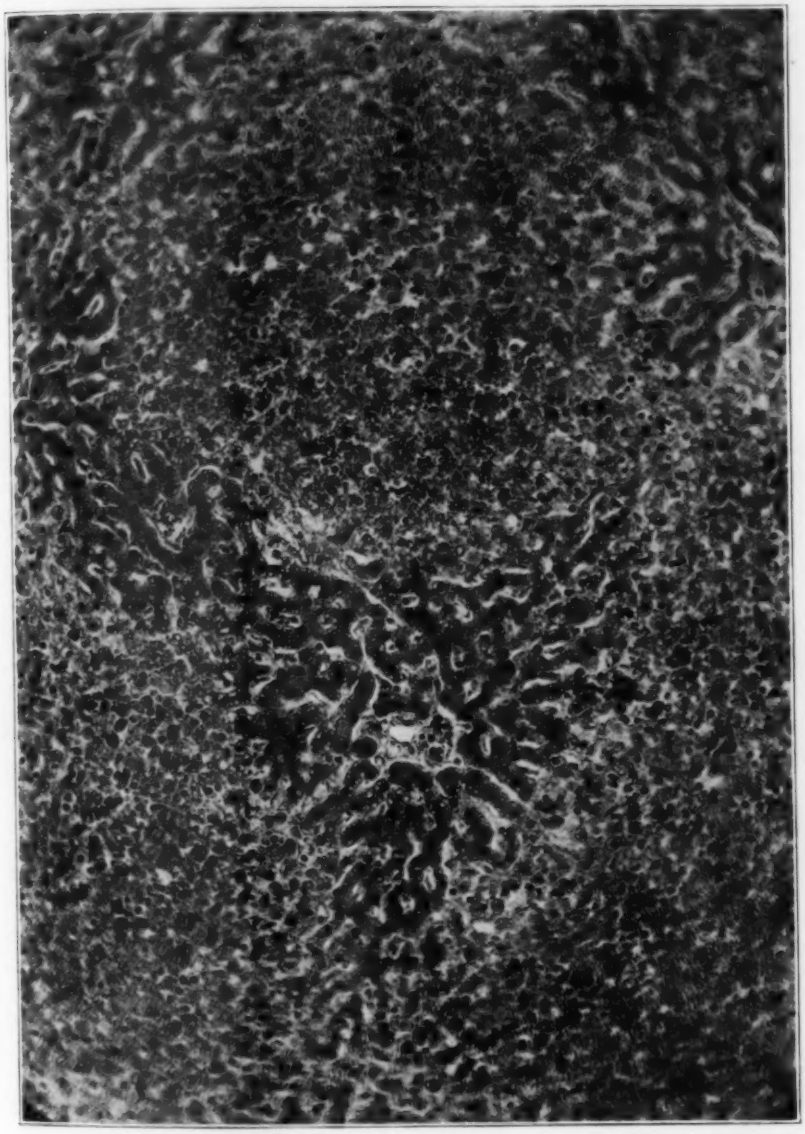

Fig. 2.—Higher magnification of figure 1, showing a portal space with vacuolations of the periportal cells and necrosis of the surrounding cells with polymorphonuclear leukocytic infiltration. × 270.

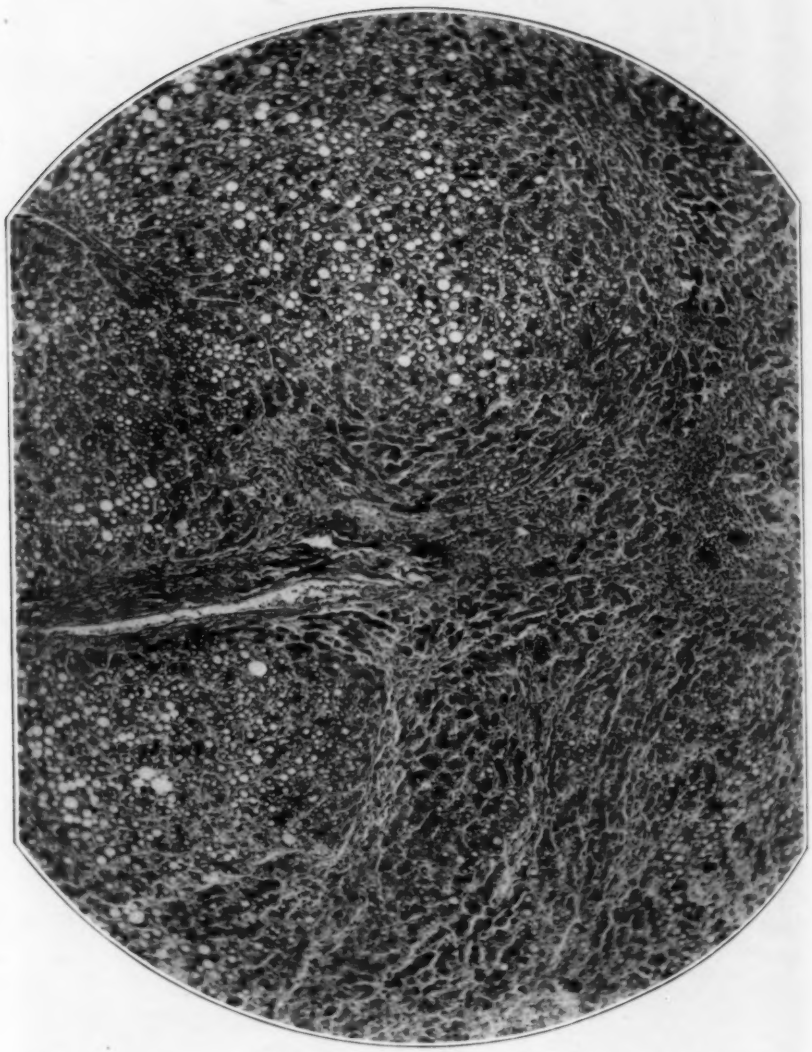

Fig. 3.—Photomicrograph of the liver in case 5, showing advanced fibrosis of a portal space and vacuolation of the central cells. × 90.

Fig. 4.—Higher magnification of figure 3, demonstrating proliferation of connective tissue and infiltration by round cells. × 270.

with mitral stenosis. After several months of preparation, the patient was subjected to a hemithyroidectomy, with the region under local anesthesia, but died on the second postoperative day from congestive heart failure. Autopsy revealed the heart as the seat of a moderate degree of mitral stenosis, with dilatation of both auricles and the right ventricle of the chronic endocarditic type, while the liver, in addition to moderate chronic passive congestion, showed advanced central necrosis of the hepatic cords not seen in the livers of patients with typical congestive heart failure. Also, there was a significant degree of periportal fibrosis as well as a moderate amount of fatty degeneration.

Case 4.—An 8½ year old white girl had suffered from hyperthyroidism for three years and on admission to the hospital had a basal metabolic rate of +52 per cent. She was prepared for operation for a five week period and then subjected to a hemithyroidectomy under cyclopropane and oxygen anesthesia. She died twenty-nine hours after the operation from a typical severe thyroid crisis. Autopsy revealed a liver weighing 850 Gm. It was grossly yellow, with the lobules showing red central zones (and yellow peripheries). Microscopically, the central three fourths of each lobule was involved in a process of acute necrosis, the viable cells being in the periportal area. These cells were markedly laden with fat. Each portal space was approximately twice the usual size, owing to proliferation of the connective tissue and accumulation of lymphocytes (figs. 1 and 2). The heart was slightly enlarged but was otherwise normal. Microscopically, a few interstitial hemorrhages between the muscle bundles were seen.

Case 5.—A 50 year old white woman had had symptoms of hyperthyroidism for fourteen years. Ten years before her admission to the hospital a subtotal thyroidectomy had been performed, with relief of her symptoms for two years. The hyperthyroidism recurred, however, and one year before admission a second thyroidectomy was performed. The patient was again well until six months before admission, when the same symptoms recurred for the second time. On admission to the hospital her basal metabolic rate was +41 per cent. After appropriate preparation the patient was operated on, under avertin with amylene hydrate and cyclopropane anesthesia. Postoperatively her course was satisfactory until the second day, when her temperature and pulse rate rose, her mental state became confused and mild icterus was apparent. Death occurred in a typical crisis sixty hours after operation. Autopsy revealed a moderate degree of jaundice and a liver which was finely nodular and weighed 1,450 Gm. Microscopically, there were advanced portal cirrhosis and a moderate degree of fatty degeneration of the remaining hepatic cells. No fresh parenchymal necrosis was evident (figs. 3 and 4).

Case 6.—A 41 year old white woman had a severe toxic nodular goiter. The symptoms were of five months' duration, and on admission the basal metabolic rate was +91 per cent. The patient was prepared for seventy-five days and was operated on under avertin with amylene hydrate and nitrogen monoxide anesthesia. On the first postoperative day she exhibited early signs of bilateral bronchopneumonia. By the thirtieth hour after the operation her condition was critical, and in spite of supportive measures she died sixty hours after the operation. Clinically, the cause of death was thought to be bilateral bronchopneumonia. This impression was confirmed at autopsy. The liver, which weighed 1,600 Gm., was slightly pale and soft. Microscopically, there were morphologic changes consisting in fatty degeneration, atrophy and granular degeneration of the cytoplasm of cells in the central half of each lobule. All of these changes ranged from slight to moderate. No necrotic cells were seen.

FUNCTIONAL CHANGES

To turn from the anatomic changes noted in the liver in cases of hyperthyroidism to studies of its functional capacity in this condition, several significant contributions deserve consideration. Hirose [6] in 1912 found that patients with hyperthyroidism exhibited a high degree of alimentary galactosuria similar to that occurring with hepatic cirrhosis and catarrhal jaundice. Sanger and Hun [7] in 1922 noted diminished dextrose tolerance in patients with hyperthyroidism and attributed this defect to failure of the liver to store dextrose properly. Youmans and Warfield [8] in 1926 employed the dextrose tolerance and phenoltetrachlorophthalein tests for hyperthyroid persons and found impaired hepatic function in 50 per cent of their entire series. Rowe [9] in 1928, using several types of tests, found impaired hepatic function in patients suffering from hyperthyroidism. Kugelmann [10] in 1930, using the levulose tolerance test, was able to demonstrate impairment of the liver's ability to convert levulose to dextrose in such patients. Heilmeyer [11] in 1931 found the urobilin quotient elevated in 50 per cent of his series of patients with hyperthyroidism. In the following year Lichtman,[12] employing the oxidation of cinchophen as a measure of hepatic function, observed slight to moderate impairment in 16 of 20 cases of hyperthyroidism. Hurxthal [13] in 1933 made use of the cholesterol test to study disease of the thyroid and found low levels in patients with hyperthyroidism, noting that the level of the blood cholesterol was inversely proportional to the basal metabolic rate and the clinical symptoms. Preoperative preparation was associated with some elevation of the level of blood cholesterol, but this was restored to normal only after operation had relieved the symptoms and had controlled the increased metabolism. Ragins [14] in 1935 found the Takata-Ara reaction positive in 6 of 14 cases,

6. Hirose, M.: Ueber die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, Deutsche med. Wchnschr. **38**:1414, 1912.

7. Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

8. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**:1 (Jan.) 1926.

9. Rowe, A. W.: Endocrine Studies: XXXV. Association of Hepatic Dysfunction with Thyroid Failure, Endocrinology **17**:1 (Jan.-Feb.) 1928.

10. Kugelmann, B.: Ueber Störungen im Kohlenhydratstoffwechsel beim Morbus Basedow, Klin. Wchnschr. **9**:1533 (Aug. 16) 1930.

11. Heilmeyer, L.: Blutfarbstoffwechselstudien, Deutsches Arch. f. klin. Med. **171**:515, 1931.

12. Lichtman, S. S.: Liver Function in Hyperthyroidism, Arch. Int. Med. **50**: 721 (Nov.) 1932.

13. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, Arch. Int. Med. **52**:86 (July) 1933.

14. Ragins, A. B.: Value of Takata and Ara Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, J. Lab. & Clin. Med. **20**:902 (June) 1935.

and Maddock, Coller and Pedersen [15] in 1936 used the bromsulphalein test and found an impairment of hepatic function in 8 of 13 cases. In the following year Althausen and Wever,[16] employing the galactose tolerance test, found a decreased tolerance in all cases and interpreted their data as evidence of impairment of the ability of the liver to convert galactose to dextrose in the presence of hyperthyroidism.

The development of the hippuric acid test for liver function as described by Quick [17] and applied to disease of the thyroid by Boyce and McFetridge,[2] Bartels and Perkin [18] and Bartels [19] made the intimate relation between the hyperthyroid state and impaired hepatic function even more apparent. Boyce and McFetridge, emphasizing the need for serial determination of the function of the liver by means of the hippuric acid test, found that the depressed hepatic function averaged 58 per cent of the normal in cases of toxic diffuse goiter at the time of the patient's admission to the hospital. With proper preoperative preparation this value rose to 66.7 per cent. Postoperatively there were a characteristic fall of approximately 6 to 8 per cent and a subsequent rise to 76 per cent of normal by the seventh day. The response of toxic nodular goiters to preoperative therapy was more favorable than that of toxic diffuse goiters, which is the reverse of the findings of Bartels. It is interesting to note that in the control cases, in which hernioplasties and elective appendectomies were performed with ethylene anesthesia, a fall from a preoperative level of 100 per cent to 79 per cent occurred in the first twenty-four hours after operation. Recovery was more prompt in those cases, however, the value reaching 91 per cent of normal by the second postoperative day.

Bartels,[19] in an extensive study of hepatic function in hyperthyroidism, stressed the following points: 1. The impairment of hepatic function is directly proportional to the severity of the hyperthyroidism, as determined by the basal metabolic rates and the clinical evidence as to the seriousness of the operative risk. 2. Only 18 of 148 patients showed normal function by the hippuric acid test. 3. The preoperative prepara-

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15. Maddock, W. G.; Coller, F. A., and Pedersen, S.: Thyroid Crisis: Its Relation to Liver Function and Adrenalin, West. J. Surg. **44**:513 (Sept.) 1936.

16. Althausen, T. L., and Wever, G. K.: Galactose Tolerance in Hyperthyroidism, J. Clin. Investigation **16**:257 (March) 1937.

17. Quick, A. J.: Conjugation of Benzoic Acid with Glycine: A Test of Liver Function, Proc. Soc. Exper. Biol. & Med. **29**:1204 (June) 1932; The Synthesis of Hippuric Acid: New Test of Liver Function, Am. J. M. Sc. **185**: 630 (May) 1933.

18. Bartels, E. C., and Perkin, H. J.: Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test, New England J. Med. **216**:1051 (June 17) 1937.

19. Bartels, E. C.: Liver Function in Hyperthyroidism as Determined by Hippuric Acid Test, Ann. Int. Med. **12**:652 (Nov.) 1938.

tion brought about a good response in hepatic function in cases of toxic diffuse goiter but little or no response in cases of toxic nodular goiter. 4. No correlation could be made between the postoperative rise in temperature and the pulse rate and hepatic function as determined by the hippuric acid test. 5. Finally, the use of a high carbohydrate, low fat diet apparently improved hepatic function, as evidenced by increased excretion of hippuric acid.

The experimental evidence for consideration of the determination of the level of the plasma prothrombin as a measure of hepatic function is as follows: Smith, Warner and Brinkhous [20] were the first to show that after use of ninety minutes of deep chloroform anesthesia as the hepatotoxin there was a precipitous fall in the level of plasma prothrombin to less than 10 per cent of normal in twenty-four hours and that the return to normal was not complete until six or seven days had elapsed. Warner,[21] after removing approximately 65 per cent of the liver of the rat, demonstrated a fall in the level of plasma prothrombin to 40 per cent of normal and a return to normal in about two and a half weeks. Lord [22] recently has shown that even gentle massage of the liver for twenty-five minutes produces a fall of 25 per cent in the level of plasma prothrombin, which is recovered from after six days. Andrus, Lord and Moore [23] and Warren and Rhoads [24] have performed total hepatectomy in the dog and observed a precipitous fall in the level of plasma prothrombin to less than 20 per cent of the normal within ten hours. All of the aforementioned workers, with the exception of Warren and Rhoads, employed the two stage titration method of Warner, Brinkhous and Smith [25] for the determination of the plasma prothrombin content. Warren and Rhoads made use of Quick's method.[26]

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20. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), J. Exper. Med. **66**:801 (Dec.) 1937.

21. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, J. Exper. Med. **68**:831 (Dec.) 1938.

22. Lord, J. W., Jr.: The Effect of Trauma to the Liver on the Plasma Prothrombin: An Experimental Study, Surgery **6**:896 (Dec.) 1939.

23. Andrus, W. DeW.; Lord, J. W., Jr., and Moore, R. A.: The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, Surgery **6**:899 (Dec.) 1939.

24. Warren, R., and Rhoads, J. E.: Hepatic Origin of Plasma-Prothrombin: Observations After Total Hepatectomy in the Dog, Am. J. M. Sc. **198**:193 (Aug.) 1939.

25. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667 (Feb.) 1936.

26. Quick, A. J.: On Various Properties of Thromboplastin (Aqueous Tissue Extracts), Am. J. Physiol. **114**:282 (Jan.) 1936.

From the foregoing observations it would seem evident that the liver is the site of formation of plasma prothrombin and that injury to the liver of varying degrees of severity is followed by a comparable fall in the prothrombin content of the plasma. Clinically, it has been repeatedly noted (Brinkhous and others;[27] Quick;[28] Butt, Snell and Osterberg,[29] Stewart and Rourke;[30] and Andrus and Lord[31]) that in diseases of the liver, such as cirrhosis and catarrhal jaundice, the level of plasma prothrombin is reduced and the response to vitamin K therapy is sluggish or absent.

The only previous reports of which we are aware recommending use of the level of plasma prothrombin as determined by the Warner, Brinkhous and Smith test for the estimation of hepatic function are those of Wilson,[32] published during the past year and a half. He found in a series of 41 patients that there was close correlation between the result of the hippuric acid test and the level of plasma prothrombin as independent measures of hepatic function. Such correlation was lacking when the galactose tolerance test was employed, as the result was normal for all of the patients studied. Wilson remarked that "in two patients with severe cirrhosis of the liver and a consistently low plasma prothrombin level of 23 and 29 per cent respectively, the hippuric acid excretion in one was only 1.2 grams, and in the other 1.9 grams, and large amounts of Vitamin K and bile salts were without demonstrable effect on the prothrombin."

We have recently reported on the use of the response of the plasma prothrombin to intramuscular injections of 2-methyl-1, 4-naph-

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27. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula: Effect of Feeding Bile and Alfalfa (Vitamin K), Am. J. M. Sc. **196**:50 (July) 1938.

28. Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A. **110**: 1658 (May 14) 1938.

29. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, J. A. M. A. **113**:383 (July 29) 1939.

30. Stewart, J. D., and Rourke, G. M.: Prothrombin and Vitamin K Therapy, New England J. Med. **221**:403 (Sept. 14) 1939.

31. Andrus, W. DeW., and Lord, J. W., Jr.: Correction of Prothrombin Deficiencies by Means of 2-Methyl-1-4-Naphthoquinone Injected Intramuscularly, J. A. M. A. **114**:1336 (April 6) 1940; Clinical Investigations of Some Factors Causing Prothrombin Deficiencies, Arch. Surg. **41**:596 (Sept.) 1940; The Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in the Treatment of Prothrombin Deficiencies, Ann. Surg. **112**:783 (Oct.) 1940.

32. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, Proc. Soc. Exper. Biol. & Med. **41**:559 (June) 1939; Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, J. Lab. & Clin. Med. **25**:1139 (Aug.) 1940.

thoquinone to differentiate intrahepatic jaundice from extrahepatic jaundice.[33] In a series of 10 patients with intrahepatic jaundice, all had reduced levels of plasma prothrombin as determined by the method of Warner, Brinkhous and Smith, the limits being 41 per cent and 76 per cent of normal. After the injection of 2 mg. of 2-methyl-1, 4-naphthoquinone, in no instance did the plasma prothrombin content rise more than 10 per cent. On the other hand, in 18 cases of extrahepatic jaundice the plasma prothrombin response to 2 mg. of 2-methyl-1, 4-naphthoquinone ranged between the limits of + 8 per cent and + 62 per cent of normal. We therefore felt that, although the initial level of plasma prothrombin might be low for several reasons (dietary insufficiency of vitamin K; poor intestinal absorption of vitamin K) and hence might not be a measure of hepatic function in many cases, the response of a lowered level of plasma prothrombin to intramuscular injection of 2-methyl-1, 4-naphthoquinone is a most sensitive measure of hepatic function.

We have followed the levels of plasma prothrombin in a series of cases of hyperthyroidism in the surgical pavilions of the New York Hospital, including 36 cases of toxic diffuse and toxic nodular goiter. No deaths occurred during the period of study. As controls we have followed (1) 10 patients with nontoxic goiter; (2) 10 patients who had undergone hernioplasties, the majority having been done with local anesthesia; (3) 9 patients who had been subjected to major intra-abdominal operations but in whom the liver had not been handled mechanically, and (4) 5 patients who had undergone operations on the brain.

From a study of these cases the following facts emerge. First, the level of plasma prothrombin in cases of preoperative hyperthyroidism shows no direct correlation with the severity of the hyperthyroidism, with the duration of the illness or with the age or sex of the patient. Likewise, the type of goiter, toxic diffuse or toxic nodular, bore no relation to the level of plasma prothrombin. However, what is apparent and perhaps more significant in the consideration of hepatic function in the patient with hyperthyroidism is the behavior of the plasma prothrombin after an operation on the thyroid gland. Postoperatively a significant fall occurred in 29 of 36 cases of toxic goiter, the degree of fall being closely correlated with the severity of the postoperative course as evidenced by the rise in temperature, the pulse rate and the clinical appearance. It happens that there was neither a

33. Lord, J. W., Jr., and Andrus, W. DeW.: The Differentiation of Intrahepatic and Extrahepatic Jaundice: The Response of the Plasma Prothrombin to Intramuscular Injection of 2-Methyl-1, 4-Naphthoquinone as a Diagnostic Aid, Arch. Int. Med., to be published.

death nor a postoperative crisis in this series, but the level of plasma prothrombin fell to 50 per cent or lower in 6 cases.

Figure 5 shows a composite curve of the plasma prothrombin in 36 cases of toxic goiter and in 10 cases of nontoxic goiter. It is of interest to note that, although there was no significant fall in the postoperative level of plasma prothrombin in the cases of nontoxic goiter, there was a postoperative rise toward a normal level of plasma prothrombin from a slightly reduced preoperative level. In contrast, the curve for toxic goiter showed slight improvement with preoperative therapy from 87 per cent to 92 per cent of normal, and after operation

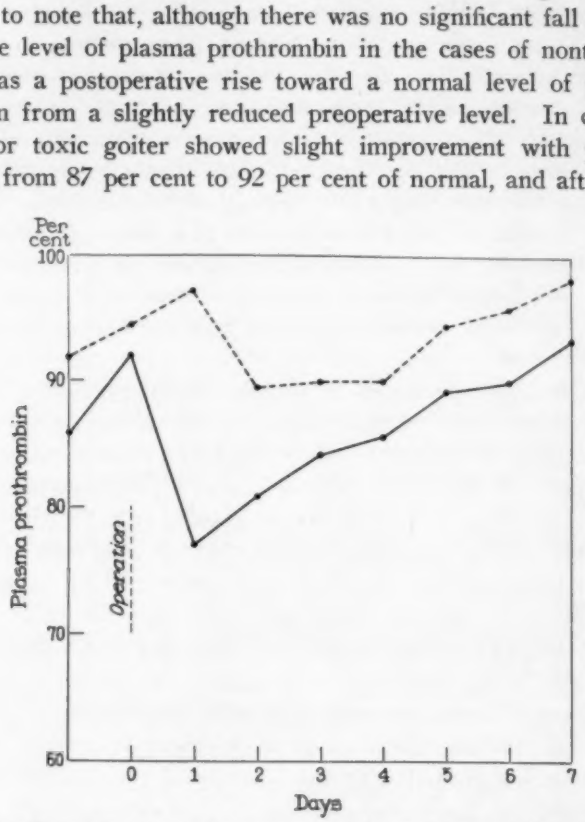

Fig. 5.—Composite curves for average levels of plasma prothrombin in 10 cases of nontoxic goiter (broken line) and 36 cases of toxic goiter (unbroken line).

a precipitate fall occurred in twenty-four hours to 77 per cent, with a subsequent return toward the normal, the level at the end of seven days being 93 per cent.

The aforementioned findings are in marked contrast to the studies on the control group. In the group of patients who underwent major abdominal operations no postoperative fall occurred. Likewise, in a group of 5 patients who underwent operations on the brain, in which moderately prolonged hyperpyrexia followed operation, an average fall of 6 per cent occurred during the first twenty-four hours, with a return to normal by the fourth postoperative day. From this it is evident that fever alone cannot explain the fall in concentration of plasma pro-

thrombin which is observed so frequently and to such a marked degree in the patients with toxic disease of the thyroid. Nine of the 10 patients on whom hernioplasties were performed showed no postoperative fall in the level of plasma prothrombin. The tenth patient, who was operated on with local anesthesia (1 per cent procaine hydrochloride), showed a moderate degree of shock during operation, with a fall in blood pressure from 125 systolic and 75 diastolic to 80 systolic and 58 diastolic, with marked apprehension and cold, sweaty skin. The patient responded promptly to the usual treatment with morphine, heat and an intravenous infusion of dextrose in saline solution. Three hours later the blood pressure was 125 systolic and 58 diastolic. The level of plasma prothrombin two hours after the operation was 50 per cent, but by the twenty-fourth hour this had risen to 90 per cent and by the forty-eighth

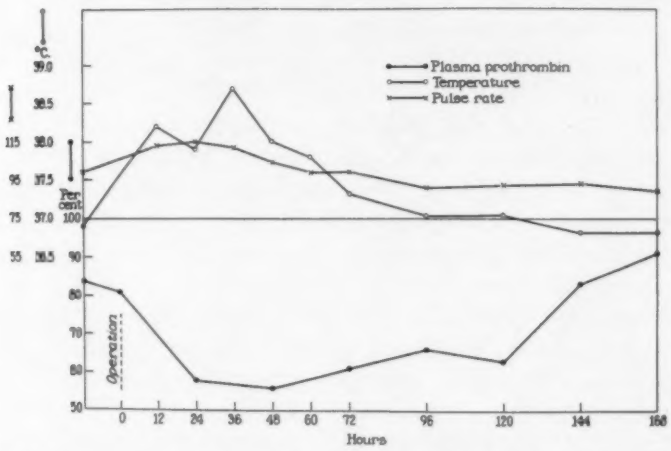

Fig. 6.—Composite curve for average levels of plasma prothrombin in 7 cases of toxic goiter.

hour to 100 per cent, indicating that no such prolonged effect was occasioned as was seen in the patients with toxic diseases of the thyroid.

Figure 6 is a composite chart of seven of the more severe postoperative reactions in the cases of hyperthyroidism studied. The fall in plasma prothrombin is correlated with the postoperative temperature and pulse rate. It is evident that the fall occurred concomitantly with the rise in the pulse rate and temperature but that full recovery in hepatic function lagged behind the return of the temperature and pulse rate toward normal. Figure 7 shows similar data on 1 case of moderately severe hyperthyroidism. The patient in this case had a basal metabolic rate on admission of + 75 per cent, which fell to 38 per cent during the preoperative stay in the hospital.

Attempted correlation of the levels of plasma prothrombin with the result of the hippuric acid excretion test was carried out in only a few cases. One of these is illustrative of the possible lack of correlation between the results of the two tests. The patient was a 37 year old white woman whose symptoms were of only six weeks' duration. On admission to the hospital the basal metabolic rate was + 80 per cent, and after one month of therapy it was + 51 per cent. Bilateral pole ligations carried out in two stages were performed, and three weeks later a determination of the hippuric acid excretion yielded a value of 3.54 Gm., at which time her basal metabolic rate was + 60 per cent. Four weeks later, before the first stage of the hemithyroidectomy, the value for hippuric acid excretion was 4.7 Gm. and the value for plasma

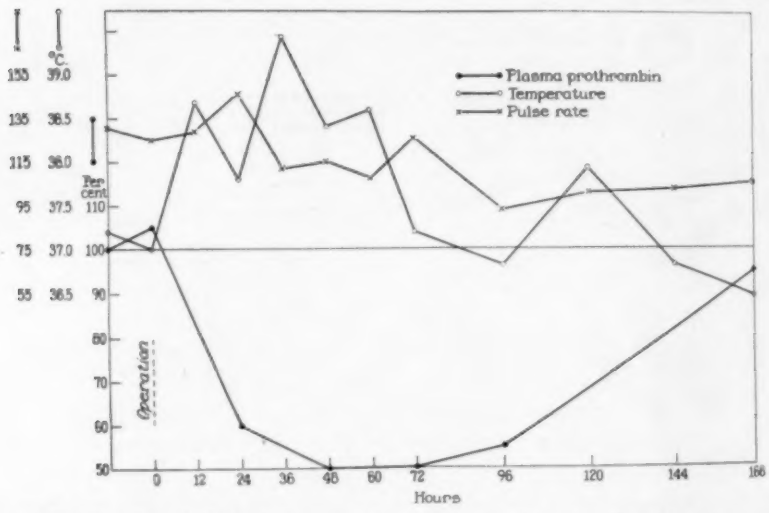

Fig. 7.—Correlation of the curve for plasma prothrombin with the postoperative reaction in a case of moderately severe hyperthyroidism. The patient was a woman aged 34 who had a toxic goiter.

prothrombin 100 per cent. However, postoperatively the plasma prothrombin fell to 50 per cent, and it had returned to only 85 per cent of normal by the sixth postoperative day. It would seem that in spite of an apparently normally functioning liver as determined by the hippuric acid test the strain of a partial thyroidectomy caused definite and significant impairment of hepatic function as determined by the level of plasma prothrombin.

Recently, a patient with a toxic diffuse goiter had marked clinical jaundice (icteric index, 50) following first stage hemithyroidectomy with local anesthesia. The temperature, the pulse rate and the patient's appearance, however, did not suggest a real crisis. Nevertheless, the

plasma prothrombin fell from a preoperative level of 61 per cent to 43 per cent of normal on the first day and 28 per cent on the third day after the operation. A subsequent rise to 60 per cent had occurred by the sixth day. The marked drop in plasma prothrombin concentration is highly suggestive of a severe degree of temporary hepatic impairment.

COMMENT

The accumulated evidence of the anatomic and functional changes in the liver in cases of hyperthyroidism suggests strongly an intimate relation between functional or even morphologic changes in the liver and severe postoperative hyperthyroid storm. How the marked pathologic changes of acute parenchymatous degeneration and necrosis come about and what causes the remarkable reduction in function as demonstrated by the hippuric acid test and the fall in the level of plasma prothrombin following thyroidectomy in cases of hyperthyroidism has not been explained. However, various factors, such as the increased metabolic demands of the body in the presence of hyperthyroidism, the decreased dextrose tolerance, the influence of a high caloric diet if this is high in fat and the postoperative febrile reaction, may all tend to increase the susceptibility of the liver to injury. Whether there is actually a circulating agent which is hepatotoxic or whether the aforementioned factors in combination are responsible for the hepatic damage cannot be answered at present. Rich [34] has shown experimentally that damage to the liver results when anoxemia and fever occur concomitantly. Although anatomic changes in the liver have been produced in rats, cats and rabbits [35] by feeding large amounts of thyroid, Youmans and Warfield [8] were unable to detect impairment of hepatic function in dogs with hyperthyroidism. On the other hand, Drill and Hays [36] have recently produced impairment of hepatic function as determined by the bromsulphalein test in dogs fed thyroid (0.6 Gm. per kilogram per day). They found that a diet adequate in yeast prevented the impairment of hepatic function and that it was the lack of yeast in the diet which led to the functional change. The foregoing findings are of great significance when considered in the light of the recent work

34. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338 (Dec.) 1930.

35. Hashimoto, H.: The Heart in Experimental Hyperthyroidism, with Special Reference to Its Histology, Endocrinology **5**:579 (Sept.) 1921. Farrant, R.: Hyperthyroidism: Its Experimental Reproduction in Animals, Brit. M. J. **2**:1363, 1913. Gerlei, F.: Nécrose du foie consécutive à l'empoisonnement par la thyroxine, Ann. d'anat. path. **10**:555 (May) 1933.

36. Drill, V. A., and Hays, H. W.: Hyperthyroidism and Liver Function in Relation to B Vitamins, Proc. Soc. Exper. Biol. & Med. **43**:450 (March) 1940.

by Rich and Hamilton [37] on the production of cirrhosis of the liver in rabbits by the deprivation of an unknown factor in the vitamin B complex. It would therefore seem advisable from the experimental evidence to supplement the diet of the patient with hyperthyroidism by administration of adequate amounts of the B complex.

SUMMARY

The important historical evidence of the morphologic damage to the liver accompanying hyperthyroidism is outlined.

In the New York Hospital series of 680 operative patients with hyperthyroidism, 16 died after operation and 6 came to autopsy. The pathologic changes in the liver are described.

The historical evidence of the impairment of hepatic function associated with hyperthyroidism is reviewed.

A series of 36 consecutive patients with hyperthyroidism and 34 controls have been studied by means of the level of plasma prothrombin as determined by the Warner, Brinkhous and Smith test. Impairment of hepatic function was noted following operation in 29 of the 36 patients in the former group.

The influence of the carbohydrate-fat ratio of the diet and of the vitamin B complex on the liver is discussed.

It is suggested that in the preparation for operative treatment of the patient with hyperthyroidism a high caloric, high carbohydrate, high protein, low fat diet supplemented with liberal amounts of vitamin B complex should be employed.

37. Rich, A. R., and Hamilton, J. D.: Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, Bull. Johns Hopkins Hosp. **66**:185 (March) 1940.

PULMONARY EMBOLISM

AN EXPERIMENTAL STUDY OF VARIATIONS IN THE VOLUME BLOOD FLOW IN THE INFERIOR VENA CAVA OF THE DOG

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AND
SIDNEY SMITH, M.S.
CHICAGO

In a publication [1] on the prevention of pulmonary embolism some clinical evidence was brought forth to support the thesis that postoperative exercises are beneficial in preventing venous thrombosis. It was assumed that simultaneous deep breaths and active leg exercises taken at regular intervals would vary the blood flow in the pelvic venous cistern and "wash out" any accumulation of blood elements which might lead to beginning formation of thrombi. Although it was definitely stated in this publication that coincidence may have been a factor, in approximately 500 cases in which the patients took postoperative exercises there was no thrombophlebitis or pulmonary embolism. In 95 control cases of fractures of the back, pelvis, hip, femur or leg requiring complete immobilization there were 5 cases of thrombophlebitis, in 3 of which there were pulmonary emboli.

It is recognized that clinical application of a principle should follow experimental studies rather than deductive reasoning. For years postoperative activity has been widely advocated but only sporadically pursued. To determine whether the reasoning back of the clinical application of postoperative exercises could be substantiated, a series of simple experiments were performed on 6 dogs. Variations in the volume flow of blood in the inferior vena cava were measured with a venturimeter. Since the results were the same in all animals, further repetition was deemed unnecessary.

APPARATUS [2]

The Venturi principle was employed in these experiments by producing partial constriction of a stiff rubber tube connected with the cut ends of the inferior vena cava (fig. 1). A "T" tube was inserted into each end of this rubber tube,

From the Department of Surgery of Rush Medical College of the University of Chicago.

1. Potts, W. J.: Pulmonary Embolism, Ann. Surg. **111**:554 (April) 1940.

2. This apparatus was perfected by Dr. Joseph Holt, of the department of physiology of the University of Chicago, who permitted its use in this study.

and to the vertical ends of the T tubes an inverted glass U tube, or differential manometer, was connected with fine, stiff rubber tubing. Variations in the height of the fluid level produced by changes in volume flow in the inferior vena cava were read from this differential manometer and by means of a hand-worked device were recorded on a smoked drum.

A pressure bottle containing sodium citrate was connected with finely drawn glass tubing to each rubber tube leading to the differential manometer. A constant fine stream of the citrate solution was thereby continuously forced toward the blood stream to prevent blood from coming into and clogging the apparatus.

It is essential that all rubber tubing be of the stiff, nonexpansile type and that all connections be absolutely tight. There must be no air in the apparatus

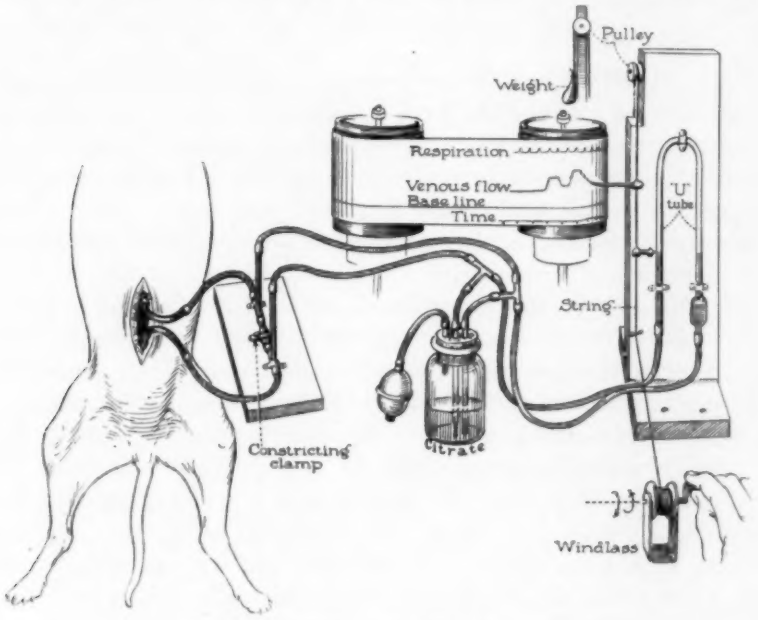

Fig. 1.—Diagrammatic sketch of apparatus.

except in the inverted U tube. The constricting clamp applied between the T tubes must be adjusted so as to produce the proper variation in the water levels in the differential manometer and must not be changed during the experiment.

By attaching the T tubes to a block fixed to the table the mechanics of the experiment were simplified and uncontrollable factors were eliminated.

A pneumograph was attached to the dog's chest, and respirations were recorded on the smoked drum exactly above the graph of blood flow.

PROCEDURE

The dog was anesthetized with pentobarbital sodium given intravenously. A cannula was introduced into the trachea to allow unobstructed breathing. The abdomen was opened in the midline and the inferior vena cava exposed from the junction of the iliac veins to the renal veins. All small veins emptying into this portion of the vena cava were tied. At this point an anticoagulant consisting

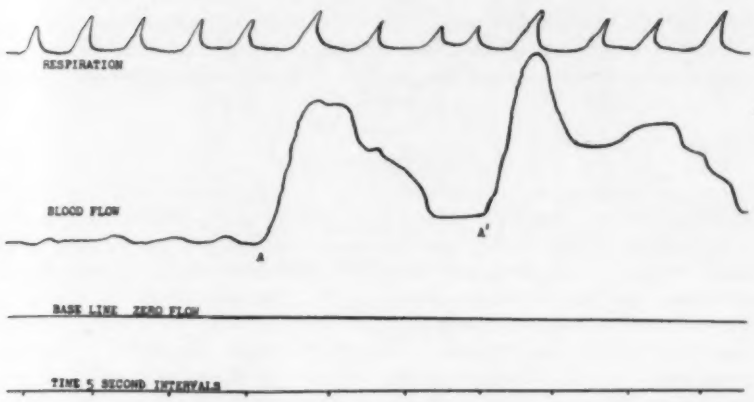

Fig. 2.—*A*, effect of elevation of both hindlegs. *A'*, effect of elevation of both hindlegs and simultaneous contraction of the leg muscles.

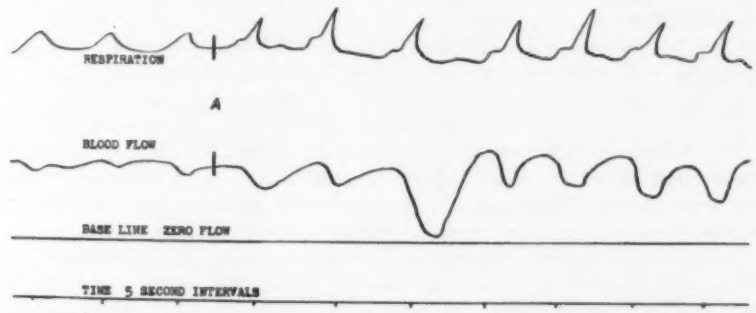

Fig. 3.—Effect of deep respirations produced with carbon dioxide inhalations begun at point *A*.

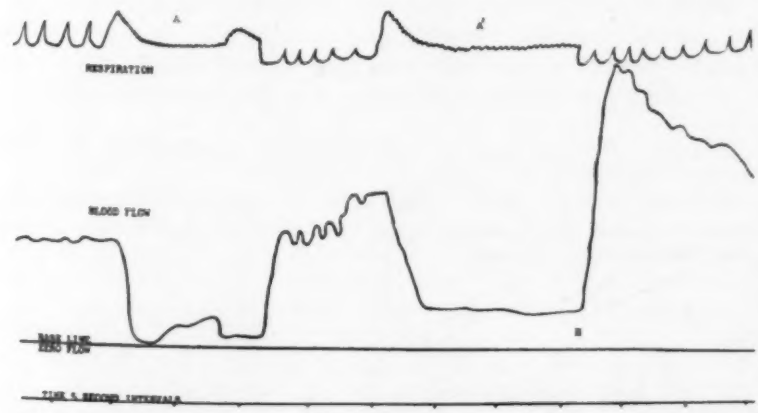

Fig. 4.—*A* and *A'*, curve with the lungs overinflated and the respirations forcibly stopped. *B*, effect of elevation of both hindlegs simultaneous with release of overinflated lungs.

of 100 mg. of chlorazol fast pink BKS [3] (trade name, fastusol pink) per kilogram of body weight was injected intravenously. Curved glass tubes the size of the inferior vena cava were inserted, one into the proximal and the other into the distal portion of the vessel. These were connected to the T tubes.

EXPERIMENTS

Simultaneous elevation of both hindlegs of the dog produced an increase varying from 100 to 150 per cent in the volume flow of blood in the inferior vena cava (fig. 2). In animals rather lightly anesthetized, contraction of the muscles in both hindlegs occurring coincident with their elevation produced an increase of more than 250 per cent in the volume flow (fig. 2). The increase in the volume flow was abrupt and returned to normal in ten to fifteen seconds. To check the accuracy of our observations, the femoral veins were isolated just below the inguinal ligament and clamped. Elevation of the legs then produced practically no change in the volume of blood flow. Removal of the clamps was followed by a prompt increase in flow.

Normal respiration caused little demonstrable alteration in blood flow. Deep respirations, however, produced by inhalation of carbon dioxide caused irregular changes in flow (fig. 3).

It has been shown by Luckhardt, Alpert and Smith [4] that the reflex inhibition of respiration will temporarily obstruct the return flow of blood to the heart. The longer the breath is held the greater will be the damming back of the venous blood. To simulate this condition the dog's lungs were overinflated by blowing on the tracheal cannula and then occluding it. Blood flow in the inferior vena cava dropped to almost zero. Release resulted in a prompt and marked rise in blood flow (fig. 4). Simultaneous elevation of the hindlegs, with deflation of the overinflated lungs, caused an enormous increase in blood flow (fig. 4).

Calibration of the blood flow in cubic centimeters in the inferior vena cava under normal and experimental conditions was determined but is of no interest here. We sought only to determine the *variations* in the volume of blood flow which could be produced.

CONCLUSION

Experimentally we have shown that breathing and leg exercise cause great variations in the volume blood flow in the inferior vena cava. Clinically we believe that deep breathing and leg exercise are of value in preventing postoperative thrombosis and pulmonary embolism.

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3. Modell, W.: Chlorazol Fast Pink BKS as an Anticoagulant, Science **89**: 349 (April 14) 1939.

4. Luckhardt, A. B.; Alpert, R., and Smith, S.: Hemodynamic and Respiratory Changes Following the Manipulation and Traction of the Gastrohepatic Ligament, Science **76**:545 (Dec. 9) 1932.

MACROSCOPICALLY NONPATHOLOGIC GALLBLADDER

A CLINICOPATHOLOGIC STUDY

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More than three fourths of all gallbladders removed contain stones, which are thought by many to cause symptoms invariably.[1] Removal of the gallbladder results in relief of symptoms in 90 to 95 per cent of cases.[2] Gross disease of the gallbladder without stones, so-called acalculous cholecystitis, also probably causes symptoms in the majority of cases, and removal of the organ is attended by relief of symptoms in 80 to 90 per cent.[2a] A third type of gallbladder occasionally encountered at operation for clinically diagnosed disease of the gallbladder contains neither stones nor any other macroscopic evidence of disease. It is this type of gallbladder with which the present report is concerned. Judd and his associates have remarked, "such cases constitute one of the major therapeutic problems of biliary surgery."[2a] Although results in the individual case are unpredictable, it has been found empirically that removal of such a normal-appearing gallbladder results in relief of symptoms in only a slightly smaller percentage of cases than in either of the two groups aforementioned. The problems of preoperative diagnosis of such a condition and, when it is encountered at the operating table, the problem of determining whether removal of the gallbladder will be in the best interest of the patient prompted the present study.

Included are those patients whose gallbladders were removed by primary cholecystectomy at the Mayo Clinic in the years 1931 to 1933,

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* Fellow in Surgery, the Mayo Foundation.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Mayo, W. J.: "Innocent" Gallstones a Myth, J. A. M. A. **56**:1021-1024 (April 8) 1911. Walters, W.; Gray, H. K., and Priestley, J. T.: Surgical Report for 1938 on Lesions of the Stomach and Duodenum, Proc. Staff Meet., Mayo Clin. **14**:807-814 (Dec. 20) 1939.

2. (*a*) Judd, E. S.; McIndoe, A. M., and Marshall, J. M.: Surgery of the Biliary System, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1931, vol. 7, chap. 2. (*b*) Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1936, vol. 3, chap. 7, pt. 2, pp. 433-472.

inclusive, and on examination in the laboratory revealed grossly a minimum of pathologic change. Among these patients, of course, are some for whom the appendix was incidentally removed at the time of primary cholecystectomy. This period represents a follow-up interval of at least five years, a sufficient postoperative interval to discount properly the benefits obtained from prolonged rest in bed, supervised convalescence, nutritious diet and so forth. Of the 1,981 gallbladders removed in this period, 81.9 per cent contained stones, and these gallbladders plus those with tumors or macroscopic deposits of cholesterol ("strawberry gallbladder") and those on which previous operation had been done were eliminated from this study, as were also those with abnormally thick walls and those that were unduly distended or markedly atrophic. Of the remaining 114 (5.75 per cent), which were to all intents and purposes normal, thin-walled gallbladders, 10 were not included in this study because of the coexistence of other abdominal

TABLE 1.—*Relative Incidence of Signs and Symptoms in One Hundred and Four Cases*

Signs and Symptoms	Number	Percentage
History of pain	88	84.6
History of colics	33	31.7
History of jaundice	31	29.8
Clinically typical of cholecystitis	54	51.9
Nervousness	49	47.1
Tenderness, epigastric or in right upper quadrant	67	64.4
History of typhoid fever	15	14.4

pathologic conditions or because of former operations which might have been reflected in the clinical course. The remaining 104 of the 114 form the basis of this report. The histories were reviewed for correlation of the symptoms, the operative findings and the pathologic change, and the results were determined through correspondence.

PREOPERATIVE FINDINGS

Age and Sex.—The average age of the patients was 41.2 years. There were 76 women, ranging from 21 to 64 years of age, and there were 28 men, ranging from 21 to 61 years of age.

Signs and Symptoms.—The average duration of symptoms was six and two-tenths years. Twenty-four patients had had symptoms for one year or less. Twenty-two had had reasons for complaint for ten years or longer. Pain, either epigastric or in the right upper quadrant of the abdomen was the most common single symptom (table 1). In many cases it was typical of biliary colic. Only half of the patients had

symptoms thought to be typical of disease of the gallbladder. In 2 who had a history of jaundice, clinical jaundice was present at the time of examination (tables 1 and 2). In the cases of 7 others a history suggestive of jaundice (dark urine, light stools and pruritus) was obtained. Those with evidence of either definite neurosis or nervous exhaustion (11 men and 38 women) comprised roughly half of any group considered, regardless of whether they were grouped according to age, according to sex or according to clinical history. A history of antecedent typhoid fever was noted for 21 to 28 per cent of persons with disease of the gallbladder in general, although recovery of the specific organism was rarely made.[3] Such a history was noted in only 8.5 per cent of one large series of routine necropsies.[4] In studies of noncalculous disease of the gallbladder the incidence has been reported as 5.53 per cent [5] and 7.1 per cent,[6] respectively. In the present study 4 men and 11 women gave a history of typhoid fever. Forty-three (56.6 per cent) of the women had been pregnant, with an average of three and six-tenths

TABLE 2.—*Findings Associated with a History of Jaundice in Thirty-One Cases*

Findings	Cases	Percentage
History of pain	28	90.3
Pain and tenderness	18	58.1
Hepatitis (surgical)	18	58.1
Pancreatitis (surgical)	7	22.6
History of typhoid fever	7	22.6

pregnancies each. More than half of the patients (53) had undergone previous abdominal surgical procedures, 48 (90 per cent) of which were appendectomies. Appendectomy and cholecystectomy had been done in 43 cases, leaving only 13 in which the appendix had not been removed.

Cholecystography.—Cholecystograms (oral) were made in 87 cases.[7] Of these, in almost 90 per cent normally functioning gallbladders were seen. In 3 of these cases the report was "with stones," although no stones were found at operation, an error of 3.4 per cent. Almost all

3. (*a*) Blalock, A.: A Clinical Study of Biliary Tract Disease, J. A. M. A. **83**:2057-2060 (Dec. 27) 1924. (*b*) Ivy, A. C., and Sandblom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115-122 (Aug.) 1934. (*c*) Judd, E. S.: Cholecystitis, Northwest Med. **25**:167-171 (April) 1926.

4. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782-793 (June) 1926.

5. Deaver, J. B., and Bortz, E. L.: Gallbladder Disease: A Review of Nine Hundred and Three Cases, J. A. M. A. **88**:619-623 (Feb. 26) 1927.

6. Muller, G. P.: The Noncalculous Gallbladder, J. A. M. A. **89**:786-789 (Sept. 3) 1927.

7. Kirklin, B. R.: Persisting Errors in the Technic of Oral Cholecystography: A Procedure Designed to Avoid Them, J. A. M. A. **101**:2103-2105 (Dec. 30) 1933.

(91.6 per cent) of the patients with a history of colic were found to have normal roentgenograms. Of those with normal cholecystograms, 28.7 per cent gave a history of colic. Because a gallbladder may be so damaged at one time as to be nonfunctioning and yet recover sufficiently to fill, concentrate and empty normally at a later date,[8] the diagnosis should not rest entirely on a cholecystographic report.[2]

OPERATIVE FINDINGS

Adhesions.—The frequency of adhesions around the gallbladder in association with disease of the biliary tract in general has been found to run as high as 73 per cent.[9] A relatively avascular peritoneal fold, described by Nagel as the "cholecystoduodenocolic fold," joins the gallbladder and the duodenum normally in 12.5 per cent of cases.[10] In the present study a third (35) of the patients had adhesions around the gallbladder. An attempt to correlate the symptoms with the operative findings was discouraging.[11] A history of either pain or colic was more frequent among patients without adhesions (88.4 per cent and 34.7 per cent, respectively) than among those with adhesions (77.1 per cent and 25.7 per cent, respectively), which absolves the adhesions from being the primary cause of either. Nor could the adhesions be attributed to previous abdominal operations, for adhesions were as frequent among those who had not had the abdomen opened previously (37.3 per cent) as among those on whom operations previously had been performed (30.2 per cent). Adhesions in the former group were probably inflammatory in origin, except for those which were due to rare congenital anomalies. Adhesions did not affect the cholecystograms, for more than 90 per cent of patients with adhesions had a normally functioning gallbladder, even a higher percentage of normal gallbladders than was noted among those with no adhesions. This supports Kirklin's statement that adhesions around the gallbladder cannot be accurately diagnosed cholecystographically.

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8. Murphy, G. T., and Bollman, J. L.: The Concentrating Activity of Bile in the Gallbladder Following Restoration from Acute Experimental Cholecystitis, S. Clin. North America **11**:917-919 (Aug.) 1931.

9. (*a*) Brown, M. J.: Non-Calculous Chronic Gall-Bladder Disease, Am. J. Surg. **41**:238-254 (Aug.) 1938. (*b*) Carman, R. D.; MacCarty, W. C., and Camp, J. D.: Roentgenologic Diagnosis of Cholecystic Disease, Radiology **2**:80-89 (Feb.) 1924. Blalock.[3a]

10. Nagel, G. W.: The Etiology and Importance of the Cystico-Duodeno-Colic Fold, Surg., Gynec. & Obst. **37**:365-372 (Sept.) 1923.

11. (*a*) Behrend, A., and Gray, H. K.: Acute Cholecystitis: Problems Created by an Attempt to Correlate Its Clinical, Surgical and Pathologic Manifestations, Surgery **3**:195-199 (Feb.) 1938. (*b*) Mayo, W. J.: Cholecystitis Without Stones or Jaundice in Its Relation to Chronic Pancreatitis, Am. J. M. Sc. **147**:469-474 (April) 1914. (*c*) Snell.[2b]

Hepatitis and Pancreatitis.—Many investigators have concluded that infiltration of the portal spaces by leukocytes can be demonstrated frequently both at operation and at necropsy, regardless of the presence or absence of biliary disease.[12] Such hepatitis has no clinical significance, is of little importance in the production of symptoms [13] and is not a factor in causing clinical cirrhosis.[12a, b] Even those who contend that there is a relation between cholecystitis and hepatitis fail to agree as to which is primary.[14] In the present study, 51 patients (49 per cent) were described by the surgeon as having hepatitis, although for none of these was the diagnosis confirmed by biopsy. This so-called hepatitis was almost as frequent among those whose appendixes had been removed (43.7 per cent) as among those who still had their appendixes when examined (53.6 per cent).

Pancreatitis in cases of "stoneless" cholecystitis has been reported by different observers as occurring in 1.2 per cent [5] and 14.4 per cent of cases.[15] In the present study pancreatitis was reported in 15 cases (14.4 per cent). Enlarged lymph nodes along the cystic and common bile ducts were present in 15 cases (14.4 per cent). The common bile duct was explored and was drained with a T tube in 2 cases. No gross pathologic lesion was found in either the stomach or the duodenum of any patient.

PATHOLOGIC PICTURE

The wall of the normal gallbladder varies in thickness from 0.75 mm. in the distended state to 2 or 3 mm. in a state of contraction.[16] Fat in the serosa may increase this thickness and may rob the organ of its bluish appearance, although there is no evidence that this is not a normal condition.[9b] Solitary lymph follicles are found in the bases of the crypts formed by the folds into which the mucous layer is thrown, seemingly by underlying corresponding ridges of connective tissue of

12. (*a*) Martin, W.: Hepatitis and Its Relation to Cholecystitis, Ann. Surg. **85**:535-554 (April) 1927. (*b*) Noble, J. F.: The Relation of Hepatitis to Cholecystitis, Am. J. Path. **9**:473-496 (July) 1933. (*c*) Mentzer.[4]

13. Snell, A. M.: Personal communication to the author.

14. (*a*) Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521-537 (May) 1918. (*b*) Matthews, A. A.: Pathology and Diagnosis of Cholecystitis, Northwest Med. **25**:171-178 (April) 1926. (*c*) Rehfuss, M. E., and Nelson, G. M.: The Problem of Gall-Bladder Infection, Am. J. Digest. Dis. **5**:571-576 (Nov.) 1938. (*d*) Wilkie, A. L.: The Significance of Hepatitis in Relation to Cholecystitis: An Experimental Study, Brit. J. Surg. **16**:214-220 (Oct.) 1928. (*e*) Noble.[12b]

15. Hartman, H. R.: Jaundice in Surgical Cholecystitis Without Stones, M. Clin. North America **7**:89-95 (July) 1923.

16. Sudler, M. T.: The Architecture of the Gall-Bladder, Bull. Johns Hopkins Hosp. **12**:126-129 (April-June) 1901. Carman and others.[9b]

the fibromuscular layer (fig. 1). In this layer of connective tissue there are rich networks of capillaries and lymphatic vessels, although the latter do not extend up into the folds. As a result, materials which pass through the mucosa into the lymphatic vessels must traverse much connective tissue and are probably carried there by the wandering cells of connective tissue. Lymphocytes may be present normally in the wall of the gallbladder even in an infant.[17] With these observations, like Noble one wonders whether many of the minimal cellular reactions seen in gallbladders removed surgically really represent a pathologic process.

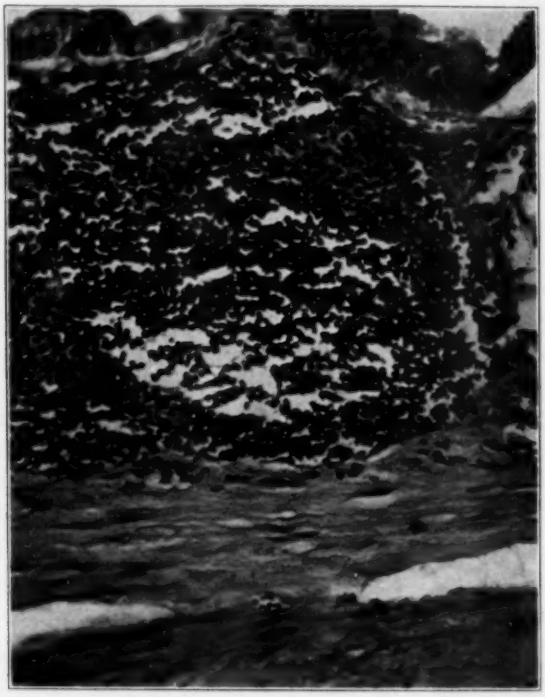

Fig. 1.—Solitary lymph follicle of the mucosa at the base of a crypt in a gallbladder which otherwise showed minimal lymphocytic infiltration.

The incidence of disease of the gallbladder as revealed by the microscope at necropsy is variously reported as from 30 to 75 per cent, and some believe that it is doubtful that any person more than 30 years of age can boast of a normal gallbladder.[18]

17. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and the Associated Pancreatitis, Arch. Surg. **4**:23-50 (Jan.) 1922. Maximow and Bloom, cited by Noble.[12b]

18. Brown, C. F. G., and Delkart, R. E.: Keto-Cholanic Acids in the Medical Management of Low Grade Gallbladder Disease, J. A. M. A. **108**:458-461 (Feb. 6) 1937. Mentzer.[4] Carman and others.[9b]

At the time of cholecystectomy these gallbladders were studied grossly and microscopically.[19] Chronic catarrhal cholecystitis of grade 1 or less (on the basis of 1 to 4) was diagnosed in 92 (88.4 per cent); in 4 of these the walls were described as slightly thickened, and pericholecystitis was diagnosed in 2 of them. In 7 (6.7 per cent) cholecystitis of grade 2 was diagnosed, and in 5 (4.8 per cent), subacute cholecystitis; in 1 of these the subacute cholecystitis was said to be superimposed on chronic cholecystitis. The absence of the diagnoses chronic fibrous cholecystitis and "strawberry" gallbladder will be noticed. For the present study, new blocks were taken from two different regions and microscopic sections made of these. The hematoxylin-eosin stain was used. Eight specimens would no longer take stain, even with "rejuvenation"; hence, the microscopic observations and the tabular material are based on 96 from which suitable sections were obtained. All showed

TABLE 3.—*Findings in Relation to the Original Pathologic Diagnosis of Ninety-Six Specimens Reexamined Microscopically*

Original Pathologic Diagnosis	Cases	Lymphocytic Infiltration			
		Minimal		Marked	
		Cases	Percentage	Cases	Percentage
Chronic catarrhal cholecystitis, grade 1 or less	84	46	54.8	38	45.2
Chronic catarrhal cholecystitis, grade 2	7	2	28.6	5	71.4
Subacute cholecystitis	5	4	80.0	1	20.0
Totals	96	52	54.2	44	45.8

some lymphocytic infiltration of the mucosa and muscular layer. These were arbitrarily divided into two groups: 1. Those with few lymphocytes scattered throughout the mucosa and muscle bundles were labeled for the sake of tabulation "minimal infiltration" (fig. 2). 2. Those with many lymphocytes throughout the wall were labeled "marked infiltration" (fig. 3). It was felt that classification into subgroups was impractical. In most of the sections the degree of lymphocytic infiltration in the mucosa was proportional to that in the muscular layer and serosa. In the few instances in which this was not true the degree of lymphocytic infiltration in the muscular layer was taken as the criterion. In most specimens the postoperative changes made impossible the identification of cellular changes in the mucosa, such as edema and degeneration.

Only rarely could a polymorphonuclear leukocyte be demonstrated outside a vessel, and that usually singly, with no other similarly situated

19. Broders, A. C.: Modification of Wilson's Fresh and Frozen Section Technic, J. Lab. & Clin. Med. **16**:734-738 (March) 1931.

cell in the section to confirm this observation. Numerous collections of polymorphonuclear leukocytes were seen within thin-walled vessels with relatively large lumens, a form of "margination of leukocytes" in vessels. The operative trauma and blood stasis incident to cholecystectomy doubtless play a large part in this phenomenon. Whether or not there are any cellular changes, either within the vessels or in the tissues of the walls, secondary to the use of dye in cholecystographic procedures I am unable to say. Certain cholecystographic dyes, probably

Fig. 2.—Mucosa and muscle layer of a macroscopically nonpathologic gallbladder in which there was minimal lymphocytic infiltration. The scarcity of lymphocytes either in or between the muscle bundles will be noticed.

owing in part to their content of iodine, are bacteriostatic and germicidal,[20] and it is only reasonable to suspect that the irritation produced by such a substance in the gallbladder, especially when concentrated and stored there for twelve to fourteen hours, will result in some signs of inflammation. The findings in the present study offer nothing in

20. Nickel, A. C.: The Bacteriostatic and Germicidal Value of Tetiothalein Sodium—N. N. R. (Tetraiodophenolphthalein), Proc. Staff Meet., Mayo Clin. 4: 178-179 (June 5) 1929.

support of this, however, as almost two thirds of those without the dye showed more than minimal cellular infiltration. Table 3 contains the various findings and a comparison of the microscopic picture with the original pathologic diagnosis. In more than half of the cases only minimal lymphocytic infiltration was present. It seems logical to conclude that chronic catarrhal cholecystitis of grade 1 or 2 and (in some cases) subacute cholecystitis, both either with or without slight thickening of the wall, mean more or less the same thing pathologically, that

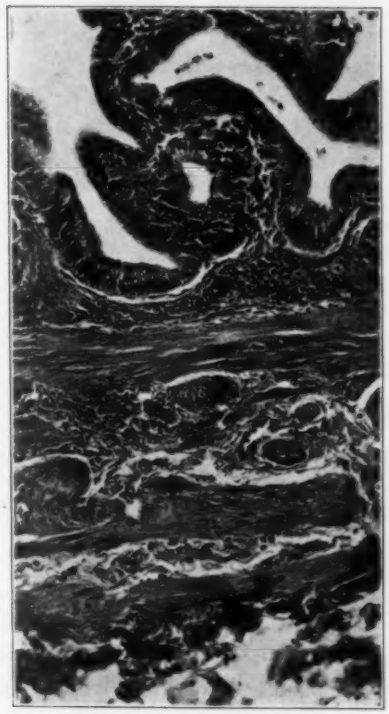

Fig. 3.—Mucosa and muscle layer of a macroscopically nonpathologic gallbladder in which there was marked lymphocytic infiltration. The numerous lymphocytes in and especially between the muscle bundles will be noticed.

is, "not far from normal," especially when these terms are used by different pathologists. It is felt that little additional information can be obtained from the microscopic examination of most gallbladders in which no pathologic condition is evident macroscopically, for all will contain a variable number of lymphocytes in the wall.

On correlation of the microscopic observations with the cholecystograms, the only thing significant is that the majority of the poorly functioning gallbladders as well as the majority of the normally functioning ones showed only minimal lymphocytic infiltration.

There is no relation between the operative findings, such as "hepatitis" and adhesions, and the microscopic pathologic appearance of the gallbladder in these cases. Marked infiltration occurred even more frequently in those without "hepatitis" than in those with this apparent hepatic change. This concurs with the views that Noble has expressed. The same is true in regard to the presence of adhesions and the microscopic picture.

MORTALITY

The mortality rate associated with cholecystectomy has been so greatly reduced that the operation is no longer regarded as hazardous. In 930 cases in which all types of cholecystectomy were done at the Mayo Clinic in 1938 the mortality was 1.82 per cent.[1b] The mortality in the present study was 0.96 per cent. The 1 death occurred on the seventh postoperative day, three days after spontaneous opening of the wound following hiccups. Follow-up letters and return visits to the clinic gave information on 91 patients, excluding the single patient who died after the operation. Six of these patients were dead at the end of five years; another died six years after cholecystectomy (table 4). The third patient listed in table 4 died eight months after operation, of carcinoma of the pancreas. This diagnosis was proved at necropsy. When cholecystectomy was done the pancreas was grossly normal, although the spleen was three times the normal size. The patient had had typical biliary colic with symptoms for ten years. It may be argued, and rightly, that the patient's original complaints were due to carcinoma of the pancreas, although we did not feel that a history of complaints extending over ten years was compatible with a diagnosis of carcinoma of the pancreas. These 7 patients were not included in calculating the results, because for only 1 (case 6) did we know the degree of relief obtained from cholecystectomy, and that patient did not live long enough before becoming ill again to allow confirmation of this.

TABLE 4.—*Information Concerning Deaths After Dismissal from Hospital* *

Case	Sex	Age at Operation, Years	Cause of Death	Time of Death, Postoperatively
1	Male	35	Separation of wound	7 days
2	Female	57	Coronary occlusion?	35 days
3	Female	39	Carcinoma of pancreas	8 months
4	Male	42	In course of herniorrhaphy	21 months
5	Male	41	Unknown	2 years
6	Male	36	Diabetes and pulmonary tuberculosis	28 months
7	Female	55	Carcinoma of bladder	51 months
8	Female	34	Anemia; splenomegaly	6 years

* Except for case 1.

RESULTS

Thus, there were 83 patients alive at least five years after the operation about whom we had information. On the basis of these we have attempted to evaluate the results, bearing in mind the preoperative complaints and the relative degree of relief obtained (table 5). Percentages are based on these 83 patients plus the 1 who died after the operation.

TABLE 5.—*Results of Cholecystectomy*

	Results									
	Good		Fair		Poor		Operative Mortality		Results Unknown	
Patients	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Dead	No Information
Men	11	52.4	3	14.3	6	28.6	1	4.8	3	4
Women	35	55.6	15	23.8	13	20.6	0	0	4	9
Totals	46	54.8*	18	21.4*	19	22.6*	1	1.2*	7	13

* Percentages based on 84 cases.

TABLE 6.—*Reported Results of Cholecystectomy for Noncalculous Chronic Cholecystitis*

			Results		
Authors	Date	Patients	Cured, Percentage	Improved, Percentage	No Relief, Percentage
Stanton	1932	90	74.5	....	....
Mackey	1934	149	29.2	29.2	36.2
Graham and Mackey (minimal lesions only)	1934	161 (57)	31.7 (19.3)	33.5 (38.6)	29.8 (36.8)
Pfeiffer	1936	43	72.0	....	....
Schafer	1936	98	74.0*	....	26.0
Brown	1936	275	39.6	31.1	25.0
Present study	1940	84	54.8	21.4	22.6

* Includes cured and improved patients.

A comparison of the results with those obtained by others who have performed cholecystectomy for noncalculous chronic cholecystitis is shown in table 6. It can be definitely said that none of the preoperative or operative findings was of much value in determining the prognosis. Regardless of how long the patients had had symptoms, roughly half of them obtained good results from cholecystectomy, and approximately a quarter of them were no better after operation than before. Most investigators agree that if a history of biliary colic is present cholecystectomy usually will give good results.[2a] Judd [2a] reported failures in less than 9 per cent of cases in which there was a history of colic,

whereas for almost half of those (46.4 per cent) without a history of colic cholecystectomy failed to give good results. In the present study approximately 80 per cent of patients who had colic were cured or benefited, whereas 75 per cent of those without colic received some benefit. Symptoms other than pain are less likely to disappear than is pain itself.[21] A "typical story" of disease of the gallbladder was not indicative of any better prognosis than was a history of vague dyspepsia. Twenty-one per cent and 25 per cent, respectively, of patients with such histories were not benefited. Even a history of jaundice seemed to have but little importance in prognosis in the present study. In 84 per cent of patients with a history of jaundice the results were fair to satisfactory, whereas 74 per cent of those who gave no such history obtained similar results.

Cholecystectomy is reported to be a failure in approximately 40 per cent of patients with a neurosis.[2a] In the present study, the results in

TABLE 7.—*Results of Cholecystectomy in Relation to Appendectomy*

Condition	Cases	Results					
		Good		Fair		Poor	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
Previous appendectomy....	36	20	55.6	6	16.7	10	27.8
Appendectomy with cholecystectomy.....	36	21	58.3	7	19.4	8	22.2
Appendix not disturbed....	11	5	45.5	5	45.5	1	9.1
Totals.....	83	46	55.4	18	21.7	19	22.9

25 per cent of the neurotic patients were poor, whereas treatment of the more stable patients was considered a failure in 20 per cent. Whether the appendix was removed or not seems to have made little difference in the results (table 7). Even the cholecystogram gave little help in making a prognosis. Seventy-eight per cent of the patients with normal cholecystograms who gave other evidence (clinical) of biliary disease were wholly or partially relieved by cholecystectomy. All 5 patients with nonfunctioning gallbladders were cured after cholecystectomy. The presence or absence of adhesions made little difference in the success of the operation, as in approximately 80 per cent of each group some relief was obtained by operation. The results were approximately the same regardless of whether or not hepatitis was observed by the surgeon.

Although there was no evident gross pathologic lesion according to the defined conditions of this study, comparison of the microscopic

21. Graham, E. A., and Mackey, W. A.: A Consideration of the Stoneless Gallbladder, J. A. M. A. **103**:1497-1499 (Nov. 17) 1934.

observations with the operative results showed good results to be equally distributed between those with minimal and those with marked cellular infiltration. In approximately a quarter of each group treatment was a failure.

COMMENT

Several questions present themselves. What effect does the removal of an apparently normal gallbladder have on physiologic function? It has been proved that the gallbladder has the same general activities as the intestine, namely, absorption, secretion and motor activity; it also concentrates bile.[22] The functional significance of the gallbladder is proved by the fact that its removal is usually followed in a few weeks by dilatation of the extrahepatic biliary tract. This dilatation is dependent on an intact sphincter of Oddi and is less when the common bile duct is drained postoperatively.[23] In dogs, cholecystectomy is soon followed by paresis of the sphincter of Oddi, which later in most instances becomes sufficiently competent to cause the extrahepatic biliary ducts to become dilated.[24] Even hypertrophy of the sphincter of Oddi may develop.[3b] The concentrating ability of the gallbladder is evidenced by its ability to prevent the development of jaundice for many hours after obstruction of the common bile duct.[23] That the pathologic functionless gallbladder can be removed without harm does not mean that removal of a normal gallbladder, which has a pressure-regulating function, is equally harmless.[25] What constitutes chronic cholecystitis, either pathologically or clinically, is not actually known.[2a] Some observers place the condition on the borderline between functional and organic disease.[26] After cholecystectomy for noncalculous chronic cholecystitis as high as 40 to 45 per cent of patients have postoperative complaints of one kind or another (table 6).[27] Reasons for this probably include

22. Ivy, A. C.: The Physiology of the Gall-Bladder, Physiol. Rev. **14**:1-102 (Jan.) 1934.

23. Mann, F. C.: A Physiologic Consideration of the Gallbladder, J. A. M. A. **83**:829-832 (Sept. 13) 1924.

24. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197-201 (July 16) 1921. Mann, F. C.: The Functions of the Gallbladder, Physiol. Rev. **4**:251-273 (April) 1924.

25. von Haberer, H.: Surgery of the Biliary Tract, Internat. Abstr. Surg. **50**:319-320, 1930; in Surg., Gynec. & Obst., April 1930.

26. Mackey, W. A.: Cholecystitis Without Stone: An Investigation of Two Hundred and Sixty-Four Operated Cases from the Clinical, Radiological, and Pathological Aspects; an Attempt to Determine the Factors of Service in Estimating Prognosis, Brit. J. Surg. **22**:274-295 (Oct.) 1934.

27. Pfeiffer, D. B.: The Indications for Surgery in Gallbladder Disease, Pennsylvania M. J. **39**:489-493 (April) 1936. Shafer, L. E.: The Surgical Treatment of the Stoneless Gallbladder, J. Iowa M. Soc. **26**:243-246 (May) 1936. Stanton, E. MacD.: The Stoneless Gallbladder: A Study of Operative Cases, Am. J. Surg. **18**:246-250 (Nov.) 1932. Broders.[19] Graham and Mackey.[21] Mackey.[26]

errors in diagnosis, residual disease either in adjacent organs or in the extrahepatic system and visceromotor disturbances, such as dyskinesia.[28]

What is the cause of the symptoms in these patients if one considers the gallbladder normal, and how does removal of this organ relieve the patient of symptoms of cholecystic disease? Inconclusive evidence exists that very slight changes in the gallbladder cause symptoms,[29] although some believe that such microscopic changes may furnish a focus from which infection spreads to other organs.[14b] Many believe that gallbladder colic may be caused by a functional disturbance of motility termed biliary dyskinesia.[28] Pilocarpine can produce spasm of the sphincter of Oddi and contraction of the gallbladder, with resultant pain, which can be relieved by the administration of atropine or of magnesium sulfate.[3b] Other possible causes of symptoms are so-called pancreatic apoplexy, with regurgitation of pancreatic juice into the gallbladder and resulting cholecystitis, and abnormally secreted bile that contains possibly too much bile salts, thus producing cholecystitis.[28a] The relief following cholecystectomy, some feel, is due to the removal of a mass of infected tissue,[15] although it is not always easy to prove that the tissue is infected.[30]

Others believe that the benefit derived from operation is due to the removal of many nerves,[31] the breaking of lymphatic pathways and the severance of adhesions around the cystic duct.[32] The operation, furthermore, enforces rest in bed and causes the patient to be careful in convalescence. Just how large a part these factors play in the results, especially in the type of cases reported in this study, is difficult to ascertain. In those cases in which the condition is due to dyskinesia, relief following removal of a normally functioning gallbladder is possibly due to paresis of the sphincter secondary to the operation.[33] Instrumental dilation of the sphincter has been suggested as an aid, but

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28. (*a*) Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy: Their Nature and Possible Significance, J. A. M. A. **105**:1093-1098 (Oct. 5) 1935. (*b*) Snell.[2b] (*c*) Ivy and Sandblom.[3b]

29. Muller.[6] Martin.[12a]

30. Andrews, E., and Henry, L. D.: Bacteriology of Normal and Diseased Gallbladder, Arch. Int. Med. **56**:1171-1188 (Dec.) 1935. Judd, E. S.; Mentzer, S. H., and Parkhill, E.: A Bacteriologic Study of Gall Bladders Removed at Operation, Am. J. M. Sc. **173**:16-23 (Jan.) 1927. Nickel, A. C., and Judd, E. S.: Cholecystitis: A Bacteriologic and Experimental Study of Three Hundred Surgically Resected Gallbladders, Surg., Gynec. & Obst. **50**:655-662 (April) 1930.

31. Womach, N. A.: Pathologic Changes in Chronic Cholecystitis and the Production of Symptoms, Surgery **4**:847-855 (Dec.) 1938.

32. Cole, W. H., and Rossiter, L. J.: Relationship of Lesions of the Cystic Duct to Gall-Bladder Disease, Am. J. Digest. Dis. **5**:576-586 (Nov.) 1938.

33. Wolfer, J. A.: Diseases of the Gallbladder and Biliary Ducts, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 7, pp. 139-224. Footnote 24.

it has been shown experimentally that scarring occurs after such dilation and that the subsequent size of the papilla is the same as before.[34] Hence, if the papilla is patent, no further dilation should be carried out. Probably the explanation of the relief obtained lies in a combination of all the aforementioned factors. But until it is known what causes the symptoms associated with grossly normal gallbladders, whether it be (1) lesions near the nerve endings, such as tension, inflammation or ischemia,[31] (2) "hepatitis," cholangeitis, pancreatitis, biliary dyskinesia or pylorospasm induced by the distended gallbladder [22] or (3) general lowering of the threshold of sensibility, little real progress will be made in evaluating the factors responsible for cure of the condition.

How can one determine preoperatively which patients will be benefited by cholecystectomy? This study would seem to indicate the impossibility of making a definite, sure prognosis. The good results were slightly higher among patients with a history of colic and a clinical picture more or less typical of disease of the biliary tract. Most of the patients with abnormal cholecystograms were benefited, but this group formed too small a percentage to be of much significance. Possibly a medical program should be tried for these patients first, as Mason and Blackford have suggested, operation being reserved for those who do not respond to medical therapy.[35] Lahey [36] has expressed the belief that if the symptoms are unrelieved by medical management the gallbladder should be removed regardless of the findings. However, in the final analysis, most important in determining which patients to operate on seems to be that intangible yet definite factor, clinical judgment.[11a]

SUMMARY

A study of almost 2,000 cases in which cholecystectomy was performed, irrespective of why it was performed, revealed that in approximately 18 per cent of the gallbladders stones were not found and that in almost a third of these (5.75 per cent of the total) there were no gross pathologic lesions and the gallbladder could not be distinguished grossly from the normal. A macroscopically nonpathologic gallbladder may be found at operation even in the presence of a history typical of disease of the gallbladder with biliary colic, jaundice and tenderness in the right upper abdominal quadrant. Half of the patients with appar-

34. Branch, C. D.; Bailey, O. T., and Zollinger, R.: Consequences of Instrumental Dilatation of the Papilla of Vater: An Experimental Study, Arch. Surg. **38**:358-371 (Feb.) 1939.

35. Ivy, A. C., and Bergh, G. S.: The Applied Physiology of the Extrahepatic Biliary Tract, J. A. M. A. **103**:1500-1504 (Nov. 17) 1934. Mason, J. T., and Blackford, J. M.: The Conservative Treatment of Cholecystitis, ibid. **99**:891-895 (Sept. 10) 1932. Brown and Delkart.[18]

36. Lahey, cited by Muller.[6]

ently normal gallbladders gave a history typical of disease of the gallbladder; one third had typical biliary colics, and one third gave a history of jaundice. I have considered several possible explanations of these symptoms, although no new evidence is offered. Half of the patients showed evidence of nervous exhaustion or neurotic tendencies. Almost 90 per cent of the cholecystograms showed normally functioning gallbladders. There was no constant relation of the operative findings to any of the preoperative findings. No evidence was found to support the view that hepatitis as described at the time of operation is of any significance in relation either to preoperative findings or to prognosis.

Microscopically, all specimens showed varying degrees of lymphocytic infiltration, although there was no relation between the degree of infiltration and the preoperative findings, the operative findings or the prognosis. The results of cholecystectomy in this study were similar to those obtained by others in similar cases, and the good results were fewer than in those cases in which definite pathologic lesions or stones were present. Fifty-five per cent of the patients were cured; 21 per cent were improved, and 23 per cent obtained no relief. The operative mortality was 1 per cent. There is no way to predict either before or at operation which patients with macroscopically normal gallbladders will be relieved of their symptoms after cholecystectomy. Regardless of the way in which the cases are grouped, approximately 1 of 4 patients received no benefit from operation.

EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

I. RELIEF OF FACIAL PAIN AND SUMMARY OF OPERATIVE RESULTS

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It has long been known from the study of pathologic conditions affecting the brain stem that there are an anatomic separation and a physiologic dissociation of the fibers of the trigeminal nerve immediately on their entry into the brain stem. The fibers conducting the modalities of pain and temperature turn downward and in company with the nucleus of the spinal tract of the fifth nerve run throughout the length of the medulla oblongata and into the upper cervical portion of the cord. During their course, they emerge from under cover of the restiform body and take a superficial position on the lateral surface of the medulla. In this situation they form a distinct elevation on the surface of the medulla—the tuberculum cinereum. In the closed portion of the medulla the tuberculum cinereum lies below the restiform body and above the olivary eminence. The fibers mediating touch sensation, on the other hand, turn upward at the point of entry into the brain stem, end in the main sensory nucleus of the trigeminal nerve and thence by the secondary neuron ascend to terminate in the sensory nucleus of the thalamus. This brief description, although it is oversimplified, of the intramedullary pathways of the trigeminal system will serve as an adequate anatomic outline to explain the basis for the procedure now known as intramedullary tractotomy.

In 1938 Sjöqvist,[1] of Stockholm, Sweden, on the basis of his studies on the organization of the central trigeminal system, proposed that section of the descending tract of the trigeminal nerve in the medulla could be used to relieve facial pain. An obvious theoretic advantage of this procedure was that touch sensation could be spared and that the face would not feel cold, stiff and numb as after section of the sensory root. A second advantage was the sparing of the motor com-

Read before the American Neurological Association, June 6, 1940.
From the Neurosurgical Service of the Hospital of the University of Pennsylvania.

1. Sjöqvist, O.: Eine neue Operationsmethode bei Trigeminusneuralgie: Durchschneidung des Tractus spinalis trigemini, Zentralbl. f. Neurochir. **2**:274 1938.

ponent. A third was the elimination of neuroparalytic keratitis, since some sensation would be retained in the eye. He also expressed the belief that such a central interruption would prevent postoperative dysesthesias. In his monograph [2] published in the same year, he reported on the results in 9 patients in whom the descending tract of the trigeminal nerve was sectioned in the medulla oblongata. Though his results in terms of relief of pain were variable, largely because the operation was a new, untried and experimental procedure, he established without question that it is possible to render the face analgetic and to relieve facial pain without grossly disturbing the sensation of touch.

Since his report there have been several other publications on the surgical results and physiologic effects of intramedullary tractotomy.[3] Last year, in a preliminary report,[4] the results of 12 intramedullary tractotomies performed in this clinic were reviewed. There are now available in the literature the observations made in 37 cases. However, little or nothing has been published on the late effects of this operation concerning either the sensory status or the neurologic sequelae. According to Sjöqvist, there are neither early nor late neurologic disturbances following the operation with the exception of paralysis of the recurrent laryngeal nerve, observed in 3 cases and thought to be due to handling of the vagal nerves during the operation. However, in his case protocols he stated that in case 4 the patient complained of numbness in the opposite side of the body and that in case 9 the patient was more ataxic after the operation than before. In Rowbottom's case 3 the patient was said to have mild ataxia of the homolateral arm following operation. In a case reported by Smyth, in which operation was performed by Jackson, the patient had disturbances in gait and ataxia of the arm.

At the time of publication of the report of 12 cases observed in this clinic, there was especial interest in exploring the possibilities of the procedure for the relief of facial pain. Little attention, therefore, was paid to the neurologic disturbances witnessed in the 12 patients, for it was assumed that they were unimportant and would disappear. Further

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2. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Acta psychiat. et neurol., 1938, supp. 17, p. 1.

3. Rowbottom, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, Brit. M. J. **2**:1073, 1938. Jackson, H., and Ironside, R.: Left Trigeminal Pain Treated by Sjöqvist's Medullary Trigeminal Tractotomy, Proc. Roy. Soc. Med. **32**:219, 1939. Walker, E. A.: Anatomy, Physiology and Surgical Considerations of the Spinal Tract of the Trigeminal Nerve, J. Neurophysiol. **2**: 234, 1939. Smyth, G. F.: The Systemization and Central Connections of the Spinal Tract and Nucleus of the Trigeminal Nerve, Brain **62**:41, 1939.

4. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498 (March) 1940.

experiences with additional cases and the opportunity to follow 15 cases over many months now permit us to evaluate the operation as a method of relief of facial pain and to describe the nature and estimate the importance of the adventitious side effects. From our experience we have concluded that certain modifications in the situation of the incision are necessary in order to avoid disturbing and sometimes permanent neurologic sequelae.

The details of the proposed modification and the anatomic reasons for it will be dealt with in a separate article. In this communication we shall deal with the immediate and late results of medullary tractotomy performed in 17 cases. In 6 of these the operation was done for major trigeminal neuralgia and in 11 for malignant disease about the head in which the presence of severe, intractable pain served as indication for operation.

SURGICAL TECHNIC AND ANATOMIC CONSIDERATIONS

A unilateral suboccipital craniectomy is performed, with removal of the posterior rim of the foramen magnum and the arch of the atlas. After the dura is opened, the arachnoid membrane of the cisterna magna is torn and the cerebrospinal fluid allowed to escape. The tonsil of the cerebellum is gently retracted until the lateral aspect of the medulla with the emerging roots of the lower cranial nerves is exposed and the fourth ventricle is visualized. According to Sjöqvist, the location of the incision is determined by identifying the lowermost vagal rootlet. At this point an incision is made into the lateral aspect of the medulla, beginning just dorsal to the rootlet and extending dorsally for 3.5 to 4 mm. The depth of the incision is 3 to 4 mm. This cut divides the descending tract of the trigeminal nerve in the tuberculum cinereum and theoretically, at least, avoids the important nuclei and tracts in this neighborhood.

Though we cannot for lack of space go into the anatomic details in this report, our experience has convinced us that this advocated level of incision is altogether too high and that it is difficult, if not impossible, to avoid injuring the restiform body or the lateral and/or main cuneate nucleus by an incision in this region. As evidence for this opinion we point to the cross-sectional illustration of the extent of the proposed incision that appears in Sjöqvist's monograph. In this figure the lower half of the restiform body is included in the transection. We feel certain that the predominant neurologic disturbances we encountered in the performance of this operation, following Sjöqvist's directions, were due largely to injury of the restiform body. In the last 3 cases we have used the obex of the fourth ventricle and the olive as the landmarks and have cut the tuberculum cinereum at a level 4 mm. below the obex and about 2 mm. below the olive. This site is 12 to 14 mm.

more caudal than that recommended by Sjöqvist. With this modification we have not observed permanent neurologic disturbances (fig. 1).

RESULTS OF OPERATION

In figures 2, 3 and 4 are summarized the data obtained from examinations of 17 patients in whom the bulbospinal tract of the trigeminal nerve was sectioned. In figure 2 are grouped the results in 6 cases of major trigeminal neuralgia, and in figures 3 and 4, the studies on the 11 cases of malignant disease about the head. In 6 cases in which operation was performed for trigeminal neuralgia we have been able to obtain repeated follow-up examinations over periods ranging from one to eleven months. In 5 cases of malignant disease treated by operation it has been possible to obtain follow-up sensory and neurologic

Fig. 1.—Prepared anatomic specimen, showing the surgical anatomy of the lateral aspect of the medulla. The stippled area outlines the tuberculum cinereum containing the descending tract of the trigeminal nerve. *X* indicates the obex of the fourth ventricle; *C.R.*, the corpus restiforme. The level of Sjöqvist's recommended incision is indicated by the line above the numeral *1*. The more caudally placed level of the incision which we advocate is indicated by the line above the numeral 2. At the latter level the restiform body may be completely avoided and the descending tract is more superficial.

examinations as indicated in figure 3. These were obtained at intervals ranging from one to thirteen months after the operation. In 6 cases of malignant disease it has been possible to obtain a considerable number of neurologic and sensory data immediately after operation, but, either because of death or because the patients were too sick to come to the follow-up clinic, late postoperative studies could not be made. In 4 of these 6 cases, as is illustrated in figure 4, we have been able to secure through correspondence with the family some scanty and fragmentary data concerning the postoperative condition of the patients during the few months of survival. As is indicated on the illustrations,

the material will be treated in terms of immediate postoperative and late follow-up results, since experience has shown that there may be considerable alteration in both the sensory status and the neurologic disturbances in the months that follow operation.

Immediate Sensory Results.—In the upper row of sensory charts in figures 2, 3 and 4 is indicated the extent of sensory loss in the face immediately following operation. All patients were examined with graduated hairs and thorns and with hot and cold tubes. The sensory

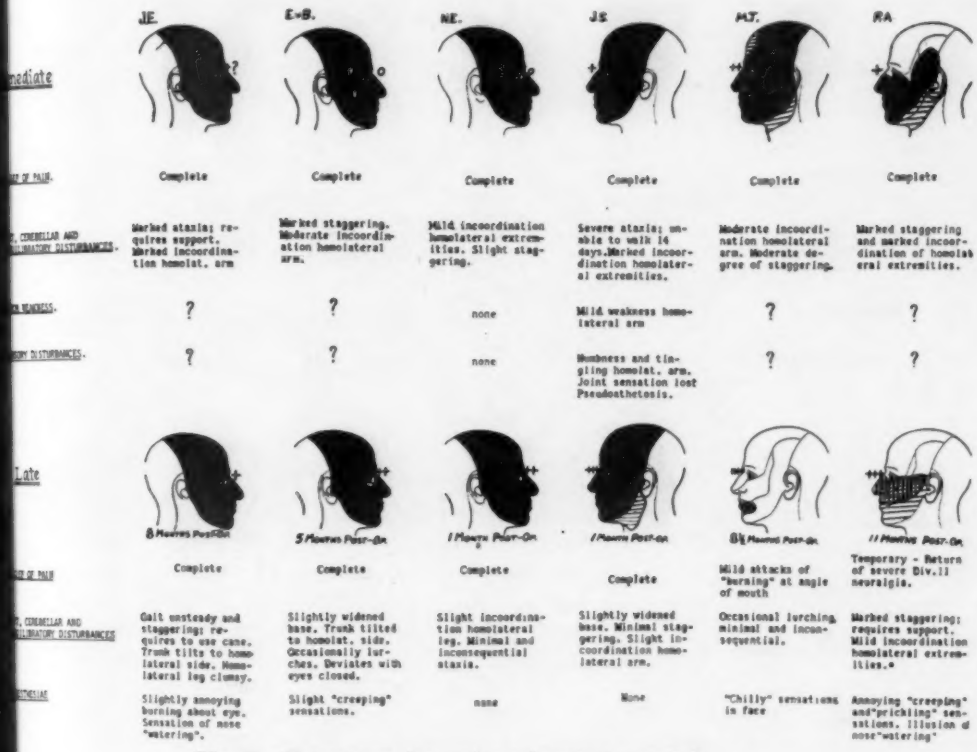
JE.
E.B.
NE.
JS
M.J.
RA
Complete
Marked ataxia; requires support. Marked incoordination homolat. arm
Marked staggering. Moderate incoordination homolateral arm.
Mild incoordination homolateral extremities. Slight staggering.
Severe ataxia; unable to walk 14 days. Marked incoordination homolateral extremities.
Moderate incoordination homolateral arm. Moderate degree of staggering.
Marked staggering and marked incoordination of homolateral extremities.
?
none
Mild weakness homolateral arm
Numbness and tingling homolat. arm. Joint sensation lost Pseudoasthetesis.
Late
8 Months Post-Op.
5 Months Post-Op.
1 Month Post-Op.
1 Month Post-Op.
8½ Months Post-Op.
11 Months Post-Op.
Gait unsteady and staggering; requires to use cane. Trunk tilts to homolateral side. Homolateral leg clumsy.
Slightly widened base. Trunk tilted to homolat. sidr. Occasionally lurches. Deviates with eyes closed.
Slight incoordination homolateral leg. Minimal and inconsequential ataxia.
Slightly widened base. Minimal staggering. Slight incoordination homolateral arm.
Occasional lurching, minimal and inconsequential.
Marked staggering; requires support. Mild incoordination homolateral extremities.
Slightly annoying burning about eye. Sensation of nose "watering".
Slight "creeping" sensations.
none
None
"Chilly" sensations in face
Annoying "creeping" and "prickling" sensations. Illusion of nose-"watering"

Fig. 2.—Tractotomy for major trigeminal neuralgia.

charts, however, deal only with the loss of pain sensation, since this is the important modality so far as the relief of pain is concerned. The solid black indicates complete analgesia, or the inability to feel as "sharp" a pressure of 40 Gm. or more with graduated thorns. The cross hatching indicates a marked hypalgesia, or the appreciation as "sharp" of 20 to 30 Gm. of pressure with graduated thorns. The linear shading indicates mild hypalgesia, or the appreciation as "sharp" of 10 Gm. or less of pressure with graduated thorns.

In 12 cases complete analgesia in the distribution of all three divisions of the trigeminal nerve immediately followed operation. In a few

instances, as is indicated on the sensory charts, there were small islands in which a few "pain points" could be found. In 2 cases (those of M. T., fig. 2 and W. S., fig. 3) there were curious combinations of analgesia and hypalgesia which did not conform to the conventional divisional territories of the face. In 1 case (that of R. A., fig. 2) the first division was entirely spared, with analgesia of the lower two divisions. In 1 case (that of C. K., fig. 3) the sensory result was unsatisfactory, there being only mild hypalgesia in all three divisions. In 1 case (that of

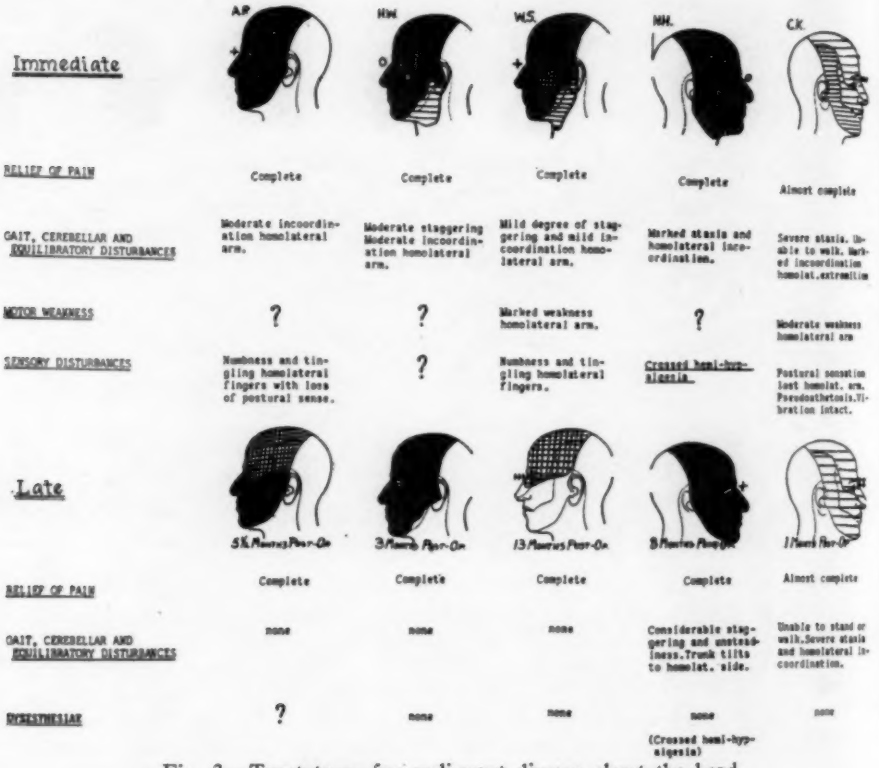

Fig. 3.—Tractotomy for malignant disease about the head.

F. W., fig. 4) the sensory loss could not be charted owing to a postoperative psychosis, but it was our impression that the impairment of sensation was slight.

On careful testing with graduated hairs, touch sensation was found to be slightly decreased in all instances in which analgesia existed, but this was difficult if not impossible to determine with ordinary cotton wool testing. The loss expressed itself as a diminution in the number of touch points per square centimeter, with or without a change in threshold.

The disturbances in temperature sensation were capricious and did not conform to the loss in pain sensibility. Sometimes with complete analgesia there was fairly good appreciation of temperature, and sometimes there was complete thermanesthesia. Occasionally heat would be appreciated but not cold, or vice versa. In an area of moderate hypalgesia, temperature might be well appreciated or, on the other hand, not at all. This agrees with the results of Spiller's [5] sensory studies, made many years ago in cases of thrombosis of the posterior inferior

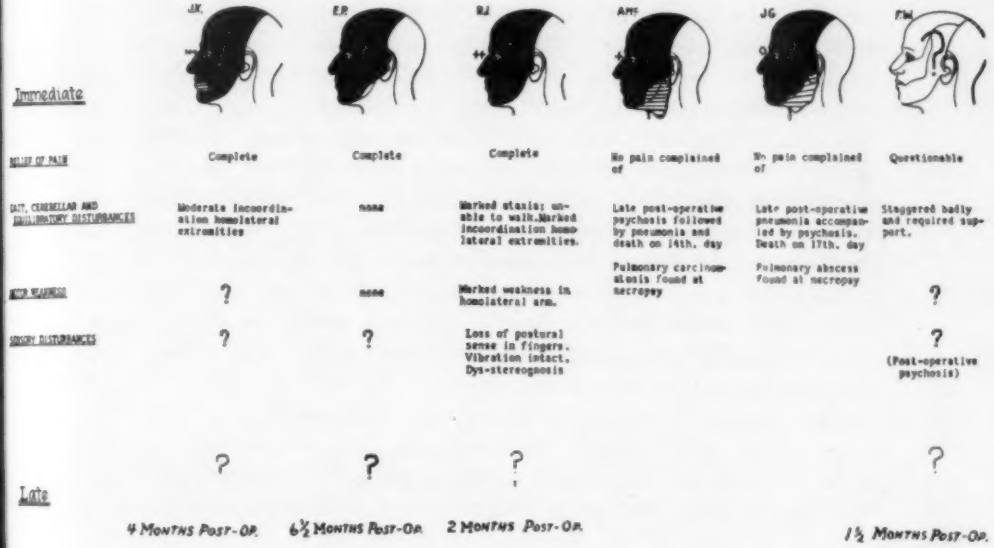

Fig. 4.—Further data on tractotomy for malignant disease about the head.

cerebellar artery, in which he found a noncorrespondence between the modalities of pain and of temperature.

It will be seen that on a number of sensory charts the disturbances in sensation extended for variable distances down the neck. This is due, as Lewy [6] pointed out, to the sensory overlap of the trigeminal field.

5. Spiller, W. G.: Remarks on the Central Representation of Sensation, J. Nerv. & Ment. Dis. **42**:399, 1915.

6. Lewy, F. H.: The Role of Cervical Nerves in Facial Sensations and the Quantitative Disturbance of Sensitivity in Major Trigeminal Neuralgia, Am. J. M. Sc. **196**:564, 1938.

Immediate Relief of Pain.—In 15 cases there was complete relief of pain following tractotomy. This included all cases of major trigeminal neuralgia. In 1 case (that of C. K., fig. 3) there was marked but not complete relief. In 1 case (that of F. W., fig. 4), in which there developed a postoperative psychosis, the result was questionable, but we feel that in this case the procedure was probably a failure. In both of these instances the sensory result was unsatisfactory.

Immediate Neurologic Disturbances.—In 14 of 15 cases in which it was possible to make postoperative neurologic examinations there were varying degrees of neurologic disturbance, ranging from very mild and transient to severe. The most evident disturbance in the early postoperative days was a wild incoordination of the homolateral arm, i. e., homolateral to the side of the medullary incision. The patient was usually unable to use the arm for feeding himself or for handling objects. The incoordination of the homolateral leg was far less. Nystagmus was present in a few instances. The static cerebellar disturbances tended to decrease and by the end of a week were slight in most cases. In several instances, however, incoordination of the arm persisted for a number of weeks. In spite of the absent or greatly diminished static cerebellar signs by the end of a week, the patient showed considerable disturbance in gait. This was, as has been stated, out of all proportion to the incoordination of the extremities that one was able to elicit while the patients were in bed. The disturbance in gait was characterized by standing with a widened base, staggering and falling to the homolateral side and a peculiar inclination of the upper part of the trunk to the homolateral side, reminiscent of the posture of a man leaning into a strong wind. By the end of two weeks these disturbances in gait had decreased or largely disappeared in most cases, but in several (those of J. E. and J. S., fig. 2, H. H. and C. K., fig. 3, and R. J. fig. 4) they persisted to the time of discharge.

In 4 cases there was weakness of the homolateral arm, which in 3 persisted past the time of discharge.

In 5 cases the patients complained of numbness and tingling in the homolateral hand and fingers, which again in 3 instances persisted until discharge. In 4 patients with this complaint who were carefully examined, loss or marked diminution of postural sensation was found in the fingers and wrists. A point of considerable interest was that vibratory sensation in these patients was intact.

LATE OBSERVATIONS AFTER TRACTOTOMY

Late Sensory Status.—In 11 cases in which late sensory examinations of the face were made one to thirteen months after operation, there were a number of alterations. Whereas in the immediate postoperative period 7 of the 11 patients who were followed showed complete analgesia of

the entire trigeminal field, late examination showed that 5 had analgesia in all three divisions. In 2 cases (those of J. S., fig. 2, and A. P., fig. 3) the analgesia had faded in the third and first divisions respectively. In 1 case (that of M. T., fig. 2) an original analgesia had almost entirely disappeared, leaving only a small patch of hypalgesia beneath the mouth. In another case (that of W. S., fig. 3), a profound degree of sensory loss in all three divisions of the face had faded to only a mild hypalgesia in the first division. About the same result was obtained in the case of R. A. (fig. 2), in which analgesia of the third and second divisions had largely disappeared, leaving moderate hypalgesia eleven months later.

It is obvious from the sensory studies on this material that the initial physiologic loss of sensation is not an exact measure of the fibers cut, nor is it possible to evaluate the sensory status until several months have passed. There is no doubt, however, that the degree and extent of loss of pain sensation is as great and as enduring with section of the bulbospinal tract as it is with section of the sensory root, provided the incision is made properly.

Late Relief of Facial Pain.—Of the 6 patients with major trigeminal neuralgia on whom operation was performed, 4 had when last seen, one to eight months after the operation, complete relief from neuralgic pains. One patient (M. T., fig. 2) complained of paroxysms of burning at the angle of the mouth, which were not distressing. However, because of the slight residual sensory loss in her face, it is possible that her neuralgia may return. One patient (R. A., fig. 2), the only patient with trigeminal neuralgia in whose case our treatment failed, had a return of severe neuralgia in the second division after relief lasting eleven months.

Of the 9 patients with malignant disease on whom tractotomy was performed and on whom we have follow-up data relating to relief of pain, 5 had complete relief one to thirteen months after the operation. Two patients (E. P. and R. J., fig. 4) had marked, though incomplete, relief. This was probably due to extension of their carcinoma to other regions of the head, outside the distribution of the sectioned trigeminal tract. Another patient (C. K., fig. 3) still had a mild degree of pain at the time of his death, one month after operation. This patient had from the time of operation an inadequate sensory loss. Another patient (F. W., fig. 4), in whom there was apparently no sensory loss produced by the operation, continued to have unabated pain, and the treatment, therefore, must be considered a failure.

Subjective Facial Sensations.—Information on the presence of subjective facial sensations was obtained only in our cases of trigeminal neuralgia. Four of the 6 patients admitted on questioning that they experienced various kinds of facial sensations although in no instance were these complained of spontaneously. However, 1 patient (J. E.,

fig. 2) occasionally took acetylsalicylic acid because of a slightly annoying burning and "sore" sensation around his eye, and another (R. A., fig. 2) rubbed his face with liniment because of prickling and creeping sensations. Two patients stated that they had creeping sensations or a chilly feeling in the face. One patient who at the end of five months stated that he had no facial sensations and is thus listed as having none (E. V. B., fig. 2) recently wrote us stating that he feels a chilly sensation on the analgetic side of his face and that when rain strikes his face it has an icy feeling.

These results are not altogether surprising, since it is well known that in the presence of thrombosis of the posterior inferior cerebellar artery, with which the descending tract of the fifth nerve is invariably involved in the softening, dysesthesias of varying kind and intensity occur in the majority of cases.[7] There is no theoretic reason why unpleasant facial sensations should not occur as frequently after tract section as they do after root section. Nevertheless, none of our 15 patients have complained of severe or distressing facial sensations.

As a matter of fact, the patients are hardly aware that their faces feel any different on the analgetic side. Only when they run the hands over the face or during shaving do they notice that the sensation is somewhat less than on the intact side. In no case were there any complaints of numbness or of thick or frozen sensations, such as are experienced after section of the sensory root.

Late Neurologic Disturbances.—In 9 of 13 cases in which data are available there were varying degrees of neurologic disturbance at intervals of one to thirteen months after the operation. In 4 instances these disturbances were minor and academic. They consisted of occasional lurching, some difficulty in walking on stairs, slight veering of gait to the homolateral side, a little clumsiness with the homolateral leg in walking or a little difficulty in performing complicated tasks, such as typewriting. In 5 cases, however, the disturbances were more severe. There were 2 such cases among those in which operation was done for trigeminal neuralgia. One patient (J. E., fig. 2) required the use of a cane to venture out on the street, although he was able to get around his house easily. He stood with a widened base; he tended to stagger to the homolateral side, and his trunk was inclined to the side operated on. Another (R. A., fig. 2) eleven months after operation was unable to walk without support. This patient, however, had symptomatic trigeminal neuralgia engrafted on multiple sclerosis. Although he had had marked ataxia of both legs before operation and it is therefore difficult to appraise the effect of the operation on the neurologic picture, the fact remains that he was more ataxic after operation than before.

7. Winther, R.: Tractotomy Viewed in the Light of the Pathology of the Medulla Oblongata, Acta psychiat. et neurol. **14**:243, 1939.

Three patients operated on for malignant disease (H. H. and C. K., fig. 3, and R. J., fig. 4) had marked neurologic disturbances. C. K. and R. J. were unable to walk without support and had marked incoordination in the homolateral extremities at the time of their death, one and two months respectively after operation. Possibly, had they survived longer, much of their neurologic disability would have disappeared. H. H. was able to walk unsupported eight months after operation but staggered considerably. There were a widened base and an inclination of the trunk to the homolateral side. He also had hemihypalgesia of the opposite side of his body; this was the only instance in our series in which there was a Wallenberg syndrome produced by the operation. Four patients (E. P., fig. 4, and A. P., H. W. and W. S., fig. 3) were entirely free of neurologic disturbances six and one-half, five and one-half, three and thirteen months respectively after operation.

Summary of Available Follow-Up Data in Fifteen Cases of Tractotomy One to Thirteen Months After Operation

	Trigeminal Neuralgia 6 Cases	Malignant Disease 9 Cases	Not Known
Complete relief of pain	4	5	
Partial relief of pain	1	3	..
No relief of pain	1	1	
Satisfactory facial analgesia	4	3	4
Inadequate facial analgesia	2	2	
Marked neurologic disturbances	1*	2	2
Moderate neurologic disturbances	1	1	
Minor neurologic disturbances	4	..	
No neurologic disturbances	..	4	
Subjective facial sensations	3	..	5
No subjective facial sensations	3	4	

* Underlying diffuse degenerative diseases of central nervous system.

Morbidity and Mortality.—There were 2 deaths in our series of 17 patients, both due to the late development of pneumonia. Both patients were examined at autopsy. One had extensive pulmonary carcinomatosis and 1 multiple pulmonary abscesses. At the time they were operated on it was felt that they would probably survive for six months, and it was thought, therefore, that an attempt to relieve them of their intractable pain was justified.

The periods of hospitalization ranged between eight and twenty-one days, with an average stay of fourteen days.

Brief mention may be made of two complications, neither of which, however, was serious. In most instances the patients complained of severe headache for one to three days, probably due to loss of cerebrospinal fluid, blood in the posterior fossa and air in the subarachnoid space. Four patients had intractable hiccups, usually appearing on the second to the fifth day and lasting three to nine days. All medica-

tion was unavailing, although temporary relief was afforded by inhalation of carbon dioxide.

COMMENT

A summary of the late results obtained in the series of 17 cases of tractotomy is found in the accompanying table. The neurologic sequelae of tractotomy as described here might seem to preclude its use. However, the suggested shift in the position of the incision into the medulla has enabled us to relieve the pain in the last 3 cases of trigeminal neuralgia with few and minor resulting disabilities. If further experience indicates that the asynergic and dysmetric complications can be reduced to this extent, a definite place exists for this procedure.

Not infrequently patients are encountered who complain of a burning sensation in the face between the paroxysms of major neuralgia. Our experience has been that frequently after relief of pain by root section this burning sensation continues as a dysesthesia in the anesthetic area. For such patients tractotomy may be particularly indicated, because the absence of subjective sensory change in the face following this procedure as compared to the total anesthesia accompanying root section may go far to prevent aggravation of the burning dysesthesia. And this persistent dysesthesia is a very distressing sequela to root section.

If a patient has trigeminal neuralgia in all three divisions, tractotomy should be considered, because the corneal reflex is spared and keratitis avoided. In the rare instances in which the neuralgia has recurred on the opposite side of the face, the initial pain having been cured by complete sensory and motor root section, the recurring pain can be relieved by tractotomy without any possibility of damage to the remaining motor root. When a cancer of the mouth, the base of the tongue or the mandible is present, requiring a suboccipital craniotomy for section of the fifth, ninth and posterior cervical roots for relief of pain, tractotomy is easier to perform than transection of the trigeminal root at the pons.

Under these limited conditions, therefore, a very real place for medullary tractotomy may be found in the treatment of trigeminal neuralgia. Because of the potential neurologic sequelae following a badly placed incision into the medulla, this procedure will never be used routinely even by those experienced with it. But every neurosurgeon dealing with many patients with trigeminal neuralgia should know how to perform this maneuver whenever the proper indication for its use exists.

FUNCTIONS OF THE EXTRAHEPATIC BILE DUCTS AND SECRETORY FUNCTION OF THE LIVER

IV. CLINICAL STUDY ON THE RELATION BETWEEN THE DUODENAL MOVEMENTS AND THE EVACUATION OF BILE INTO THE DUODENUM DURING FASTING

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Ganter [1] observed the movements of the duodenum in man by the use of the balloon method. Weitz and Vollers,[2] Peiper and Isbert,[3] Konishi [4] and others have conducted studies by the same method. Studies on the flow of bile into the duodenum during fasting have been made by numerous investigators since Einhorn devised the duodenal drainage method. Lyon [5] reported that during fasting the bile normally is not seen in the duodenal drainage fluid and when seen indicates a pathologic condition in the biliary tract. Inoue [6] observed in his studies that the bile was generally expelled continuously and rarely in a periodic manner. Iwanaga [7] reported that in man the bile was seen in the duodenal drainage fluid, while experiments on dogs (duodenal fistula) showed that generally an outflow of bile did not occur during fasting and occurred rarely in the so-called "periodic outflow" for two to seven minutes at intervals of one to two hours. He assumed that these differences observed in man and animals were probably due to the mechanical stimulus of the duodenal drainage.

In order to study simultaneously the relation between the movements of the duodenum and the discharge of bile in man during fasting, we devised a method by which we have been able to obtain excellent

From the First Surgical Clinic, Kyushu Imperial University.

1. Ganter, G.: Arch. f. d. ges. Physiol. **201**:101, 1923.
2. Weitz and Vollers, W.: Ztschr. f. d. ges. exper. Med. **52**:723 and 747, 1926.
3. Peiper, A., and Isbert, H.: Jahrb. f. Kinderh. **119**:291, 1928; **120**:48, 306 and 312, 1928; **122**:263, 1928.
4. Konishi: Jap. J. Exper. Gastroenterol. **11**:144, 1936.
5. Lyon, B. B. V.: Diagnosis and Treatment of Disease of Gallbladder and Biliary Ducts, J. A. M. A. **73**:980 (Sept. 27) 1919.
6. Inoue: Kyotogaku Zasshi M. J., 1923, vol. 20, nos. 1, 2, 3, 4, 9 and 10.
7. Iwanaga, H.: J. Jap. S. A. **25**:1004, 1924.

and often conclusive results. The method is as follows (fig. 1): A drainage tube about 100 cm. long, made up of an outer and an inner tube, was used. A balloon (7 to 8 cm. in length) was connected to the tube, together with a metallic olive. The duodenal tube was marked at points 60 and 75 cm. from the metallic olive. The outer tube was used for inflating the balloon, while the duodenal fluid flowed out through the inner tube. In figure 1, *A* is the outlet from which the duodenal fluid dripped. The amount was measured by kymographic recording of the fall of the drops. Further, the amount which fell during periods of five to ten minutes was measured, and quantitative determination of

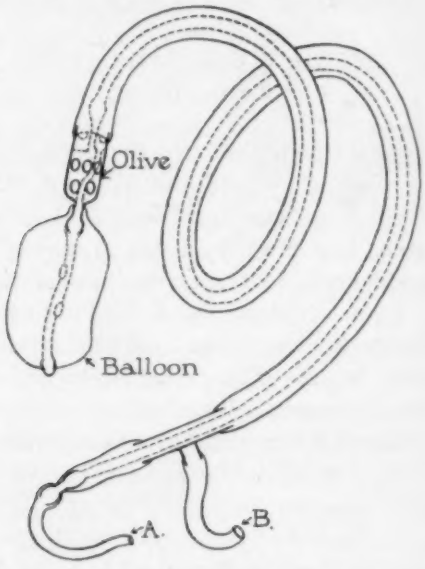

Fig. 1.—Apparatus used. See text for description.

the concentration of bile pigment (Meulengracht's method) was carried out. In the same figure, *B* leads out from the balloon in the duodenal cavity and is connected with the tambour, making it possible to record the movements simultaneously with the measuring of the drops of duodenal fluid.

A brief outline is given of the results obtained. The subjects were given a light meal on the night before investigation, and no food was given in the morning. The observations began at 9 a. m.

PERIODIC TYPES OF ACTIVITY

Case 1 (third observation, Oct. 10, 1935).—The subject was a man aged 44. As may be seen in figures 2 and 3, this subject showed typical periodic activity in both the duodenal movement and the outflow of bile. In curve 1, for the resting

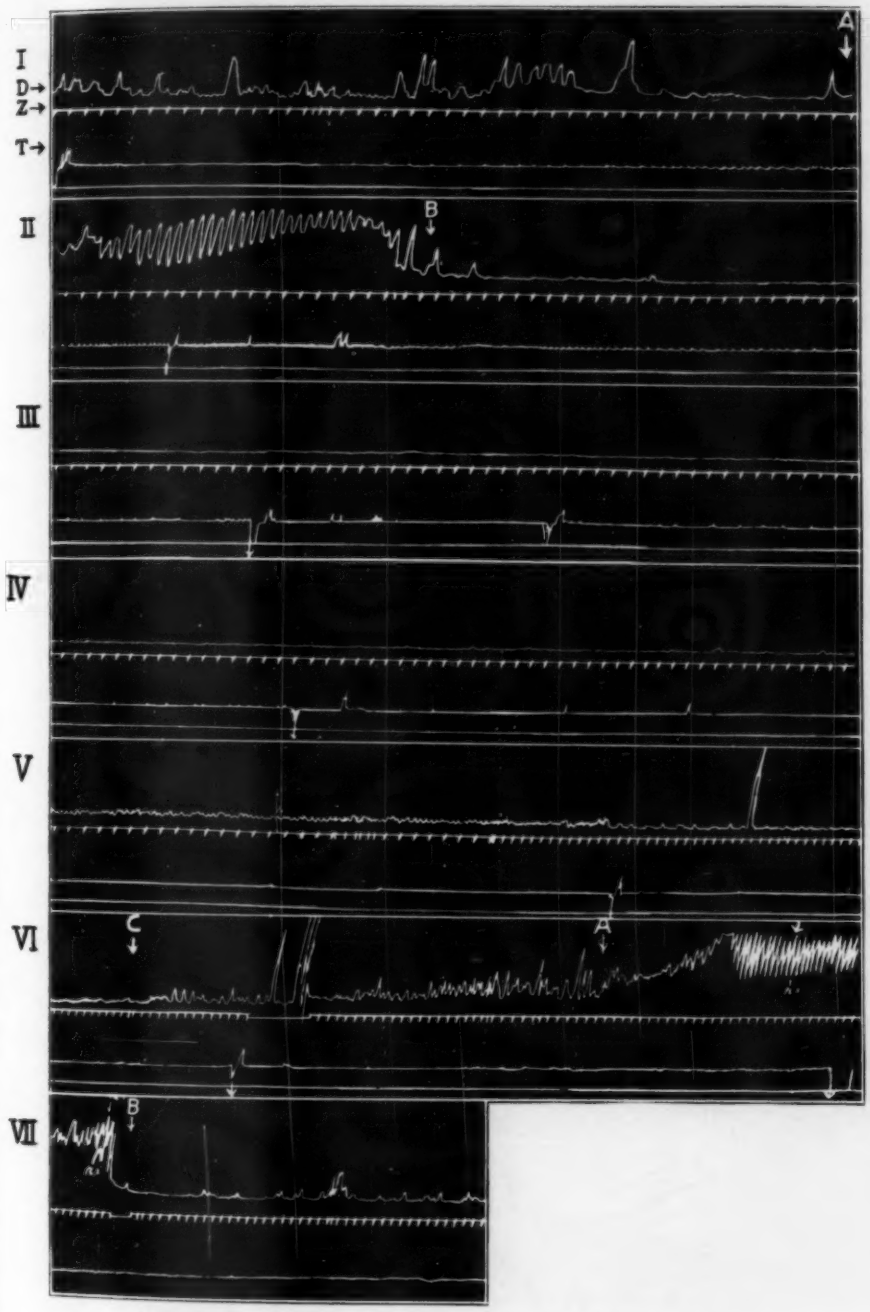

Fig. 2.—I, II, III, IV, V, VI and VII are connecting. *D*, duodenal movement; *Z*, time (ten seconds); *T*, drops of duodenal fluid.

period, that is, from *B* to *C*, the duodenum was almost inactive and only slight waves of respiration were seen. The active period, that is, from the start of the curve to *A* and from *C* to *A'*, showed that at the beginning short waves of 2 to 3 cm. in groups of two to three waves occurred at intervals; then the height of the waves and the grouping of the waves gradually increased, so that the resting intervals were shortened. In this period the resting and active movements occurred intermittently, so that it may be also said to be the intermittent active period. The period of tetanic movement is the period from *A* to *B* and from *A'* to *B'*.

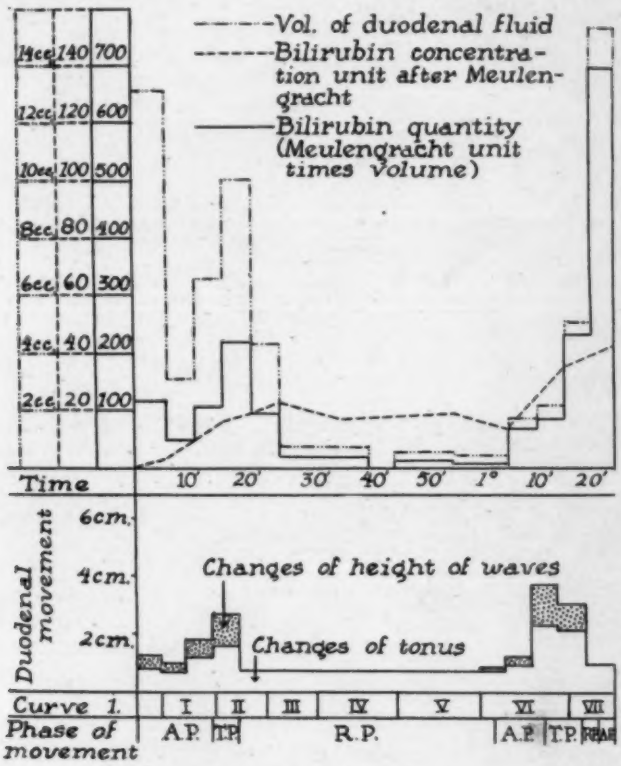

Fig. 3.—Duodenal movements and discharge of bile in case 1.

During this the levels of tonus rose suddenly and strong peristaltic waves numbering about thirty to sixty occurred continuously. The tetanic movement ceased suddenly and passed into the resting phase. With regard to the flow of bile into the duodenum, as may be seen in figures 2 and 3, the quantity of bile increased gradually up to the beginning of the tetanic period. When the duodenal movements passed from the tetanic to the resting phase, the quantity of bile decreased suddenly and the drops of duodenal liquid almost ceased. After the resting period, with the duodenal movements again active, the outflow of bile also increased. In this case, almost the same results were obtained on the second (October 3) and the fourth (October 21) observations, but the first observation did not show the periodic type of activity.

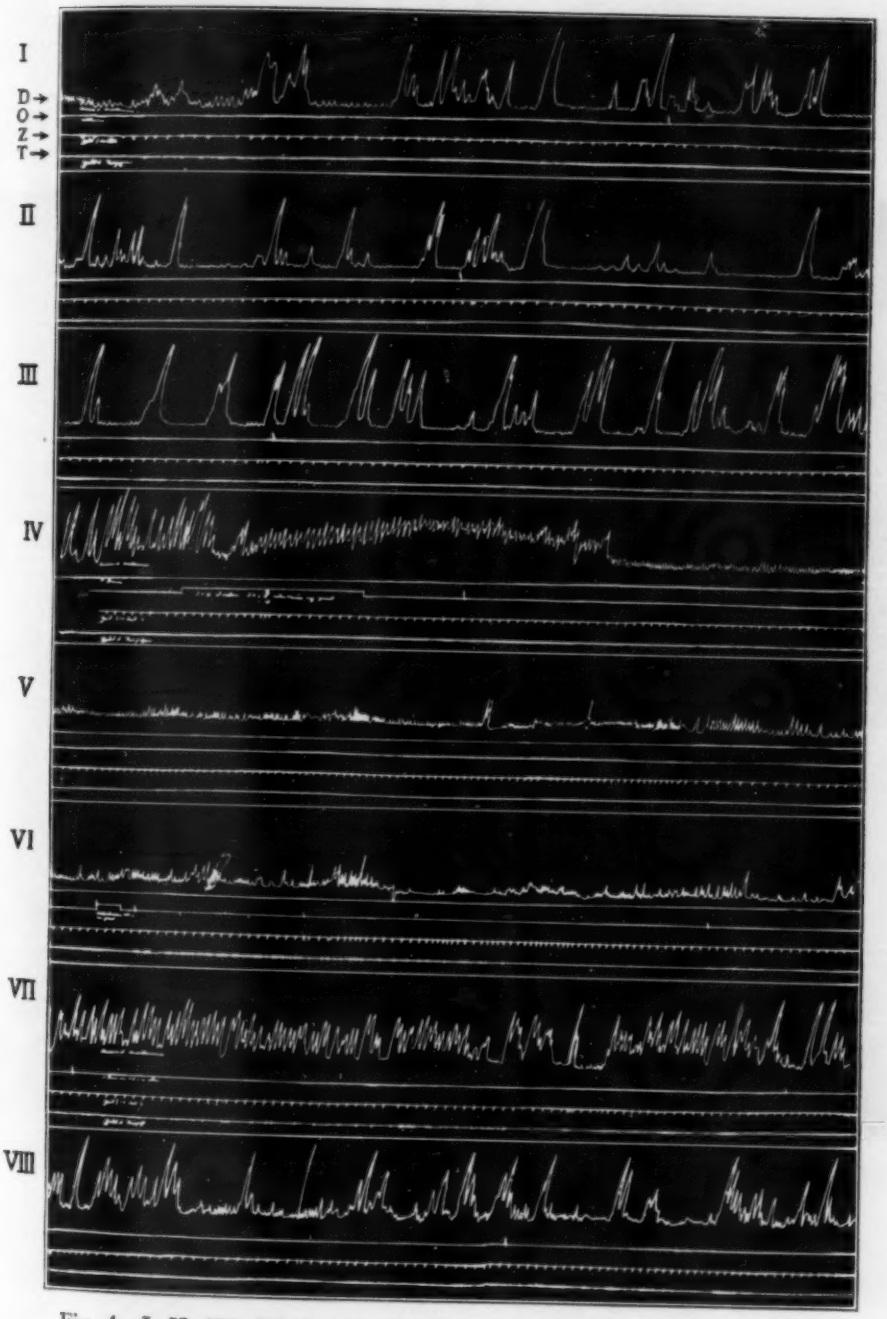

Fig. 4.—I, II, III, IV, V, VI, VII and VIII are connecting. *D*, duodenal movement; *O*, zero pressure line; *Z*, time (ten seconds); *T*, drops of duodenal fluid.

Case 2 (Aug. 13, 1935).—The subject was a man aged 44. As may be seen in figure 4, the duodenal activity showed periodic movements. The active phase lasted forty-five minutes; then the tetanic phase set in and continued for eight minutes, followed by a resting period of forty minutes, with a return to the active phase. With regard to the outflow of bile, the volume of duodenal drainage and the bilirubin content and its concentration gradually increased parallel from the

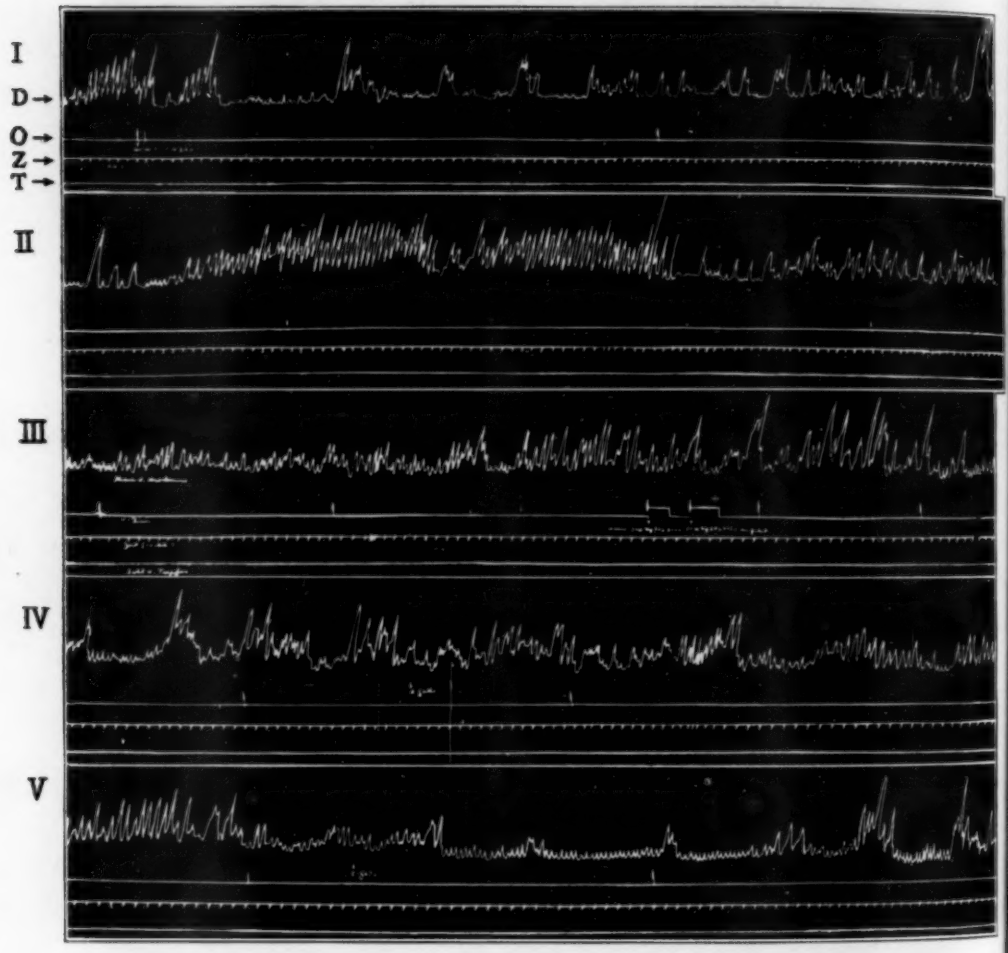

Fig. 5.—I, II, III, IV and V are connecting. *D*, duodenal movement; *O*, zero pressure; *Z*, time (ten seconds).

beginning until the middle of the tetanic period, according to the increased duodenal movements. The flow of bile ceased suddenly at the end of the tetanic period and also during the resting period. Duodenal movements occurred again twice; the fluid also flowed again, and its quantity and the concentration of bile increased gradually.

In 4 other cases almost the same results were obtained.

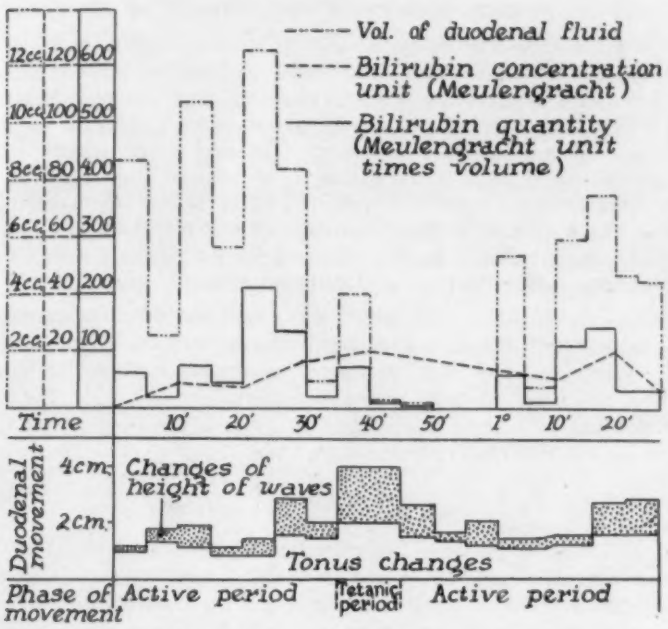

Fig. 6.—Duodenal movements and discharge of bile in case 7.

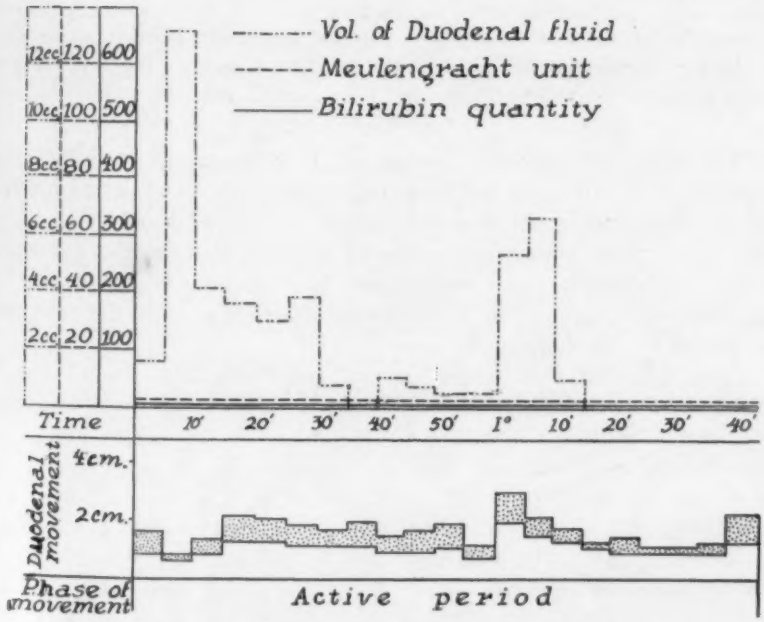

Fig. 7.—Duodenal movements and discharge of bile in case 11.

NONPERIODIC TYPES OF ACTIVITY

CASE 1 (same subject as shown in figure 2; first observation, Sept. 20, 1935).—In this case, in the second, third and fourth observations periodic activity was observed, but on a different day, although under the same conditions, a nonperiodic type of activity was observed. As may be seen in figure 5, from the beginning the duodenal movement gradually became active, and after twenty minutes the tetanic movements occurred, but with the passing of the tetanic phase the resting phase did not appear and the movement continued to be active. With regard to the outflow of bile, a gradual increase from the start was seen, both in volume and in quantity of pigment; then a decrease occurred for the tetanic period, followed by another increase during the periods of duodenal activity.

CASE 7 (Feb. 28, 1936).—The subject was a man aged 28. The quantity of bile and its concentration increased gradually with the increase in duodenal activity (fig. 6). When the tetanic movement appeared, the bile outflow diminished; then it increased again with the next period of activity.

Investigations in 3 other cases (cases 8, 9 and 10) showed almost the same results as did the first observation in cases 1 and 7.

ABNORMAL TYPES OF ACTIVITY

CASE 11 (Sept. 16, 1935).—The subject was a man aged 48. The duodenal movement was continuous (fig. 7), and there were no resting periods, as was also noted with the nonperiodic types of activity. But the duodenal fluid on examination showed no bile pigment throughout the period of investigation. Drainage was tried repeatedly, but only a cloudy fluid was obtained and no bile was observed. Cholecystographic examination was carried out and showed an abnormally large shadow of the gallbladder. After administration of two egg yolks the gallbladder contracted. In this case we assumed that the hypertonic function at the distal end of the choledochus had checked the evacuation of bile into the duodenum during the period of fasting.

COMMENT

The investigations were carried out 14 times on 11 subjects, all in normal health. In 8 investigations in 6 cases a periodic relation between the duodenal movement and the outflow of bile was observed. In 5 cases there were nonperiodic types of activity, that is, the duodenum moved continuously, with intermittent flow of bile, and in 1 case no bile pigment was found in the duodenal drainage despite the continued movement of the duodenum.

Lyon asserted that under normal conditions bile should not be observed in the duodenal drainage fluid during fasting and that, when observed, it indicates a pathologic condition of the biliary tract. In our examinations, however, bile was observed in 10 of 11 cases. In the 1 case in which bile was not observed in the duodenal fluid and the unusual size of the gallbladder was ascertained by cholecystographic examination, the gallbladder was seen to decrease remarkably in size after digestion of two egg yolks. This fact seems to indicate that the gallbladder was in a dilated condition due to the stagnation of bile. Moreover, from our experimental studies on the mechanism of bile

evacuation (to be published later) it has been ascertained that when there was no evacuation of bile into the duodenum during fasting the resistance at the distal end of the common bile duct showed over 300 mm. of water pressure, so that despite the continued contractions the gall-bladder was not able to contract over the resistance pressure, and therefore the bile could not evacuate into the duodenum. From these facts we believe that when no bile is observed in the duodenal fluid during fasting an abnormally stagnant condition of the biliary tract is indicated.

Details regarding the relation between the periodic movements of the duodenum and the outflow of bile are shown in the accompanying table. The period of activity varied from eight to sixty-three minutes; the tetanic period, from three to eleven minutes, and the resting period, from three to forty-five minutes. The periods were never constant

Relation Between Periodic Duodenal Movements and Outflow of Bile

Case	Subject's Age	Date	Active Period, Minutes	Tetanic Period, Minutes	Resting Period, Minutes
1	49	Oct. 3, 1935	Over 10	3	23
			38	11	9
1	49	Oct. 10, 1935	Over 13	5	45
			8	7	3
1	49	Oct. 21, 1935	Over 30	11	34
2	44	Aug. 13, 1935	Over 46	7	Over 14
			63		
3	34	July 1, 1935	Over 33	7	Over 20
4	38	July 16, 1935	Over 27	7	Over 17
5	54	May 21, 1935	Over 60	7	Over 15
6	50	May 20, 1935	Over 50	5	Over 5

and varied greatly even with the same subject. Especially in case 1, on October 10, the first resting period was forty-five minutes, while the second was only three minutes. The subject in this case showed also a type of movement intermediate between the periodic and the nonperiodic. On October 3 and 21 periodic types of movement were seen, while on September 20 a typical nonperiodic type was seen. The same thing can be noted in the active and in the tetanic period.

With regard to the periodic outflow of bile into the duodenum, Inoue [6] observed that outflow of bile pigment in the duodenal drainage was generally continuous and rarely periodic. Iwanaga [8] observed the same fact and assumed that it was due to the stimulus of the duodenal drainage tube. In our examinations, however, bile pigment normally appeared both periodically and continuously, even as the movements of the duodenum are both periodic and continuous. These two types cannot essentially be distinguished, and a number of intermediate types

8. Iwanaga, H.: Central Org. Jap. M. Sc. **20**:883, 970, 1056 and 1135, 1926.

are to be noted in the same subject examined under uniform physiologic conditions. Further details of these investigations will be given in our next paper.

With regard to the relation of the outflow of bile and the duodenal movements, it was noted that when the duodenum moved periodically during fasting the evacuation of bile was also periodic and that, while a flow of bile was seen during the active and the tetanic period, it ceased during the resting period. When the duodenum moved continuously, the evacuation of bile was also continuous, but rarely was any bile pigment observed.

CONCLUSIONS

1. During fasting the movement of the duodenum is periodic or nonperiodic. In the former there are three phases, active, tetanic and resting, repeated regularly. In the latter the movement of the duodenum is continuous, changing from the active to the tetanic phase, with no resting phase.

2. The outflow of bile during fasting was seen only during periods of activity of the duodenum; when the duodenal movement was periodic, the outflow of bile was also observed to be periodic, no bile flow being observed during the resting period. When the duodenal movement was continuous the outflow of bile was irregular but almost continuous.

3. In regard to periodic and nonperiodic movements, it is difficult to distinguish them essentially, and each shows varied changes due to numerous physiologic factors, so that it cannot be readily said which is normal and which is abnormal.

4. When no bile is observed in the duodenal drainage fluid despite continued movement of the duodenum during fasting, it may be assumed from this fact that a pathologic condition exists in the biliary tract. The resistance at the lower end of the common duct is high; that is, "hypertonic dyskinesia" of the biliary tract is indicated unless a complete obstruction of the biliary tract is observed.

FUNCTIONS OF THE EXTRAHEPATIC BILE DUCTS AND SECRETORY FUNCTION OF THE LIVER

V. EXPERIMENTAL STUDY ON THE RELATION BETWEEN THE MOVEMENTS OF THE DUODENUM AND THE FUNCTIONS OF THE BILIARY TRACT DURING FASTING

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The results of a study of the relation between the duodenal movements and the evacuation of bile into the duodenum in man during fasting have been given in a previous paper. However, in order that the present experimental work may be seen in proper correlation with the previous investigations, a brief outline of the latter will be given. It was found that when the movement of the duodenum was periodic the evacuation of bile was also periodic and that the evacuation occurred only during the active and tetanic periods of duodenal movement and was not seen during the resting period. When the duodenum moved continuously, bile was found in the duodenal drainage in all cases except 1, in which no bile pigment was found, although the duodenum continued active. This brings up the question: What mechanism causes the bile to evacuate periodically and nonperiodically only during the active periods of duodenal movement and to cease during the resting periods? Also, what is the explanation when no bile is seen in the duodenal fluid even though the duodenal movements are continuous? Concerning these phenomena, Boldyreff [1] stated the belief that during the period of activity of the stomach and the other digestive organs there should be contraction of the gallbladder causing evacuation of bile. Hosono [2] confirmed Boldyreff's opinion and explained that at the end of the resting phase of the stomach and the beginning of the active phase the gallbladder contracts and the sphincter of Oddi relaxes. However, several defects may be seen in the experiments carried out by these workers, and the phenomena of biliary functions cannot be fully explained by experiments on the obvious mechanisms.

From the First Surgical Clinic, Kyushu Imperial University.

1. Boldyreff, W. N.: Ergebn. d. Physiol. **29**:485, 1929.

2. Hosono, S.: Jap. J. Exper. Gastroenterol. **7**:127, 148, 171, 189 and 212, 1932.

In this paper we wish to give the results obtained in our investigations on the evacuation of bile, the contraction of the gallbladder, the resistance of the sphincter of Oddi and the duodenal movements in fasting unanesthetized intubated dogs, with the observations made almost simultaneously. The methods used in our work have been given in a previous paper and will be only briefly given here. Double intubation of the common duct was carried out without injury to the gallbladder, and at the same time a duodenal fistula was made or a small balloon was placed inside the duodenal wall opposite the papilla of Vater. In figures 1, 2 and 3 are shown the apparatus used. By the use of the apparatus shown in figure 1 the changes in intracholedochal pressure, the flow of bile into the duodenum and the movements of the duodenum were recorded. With the apparatus shown in figures 2

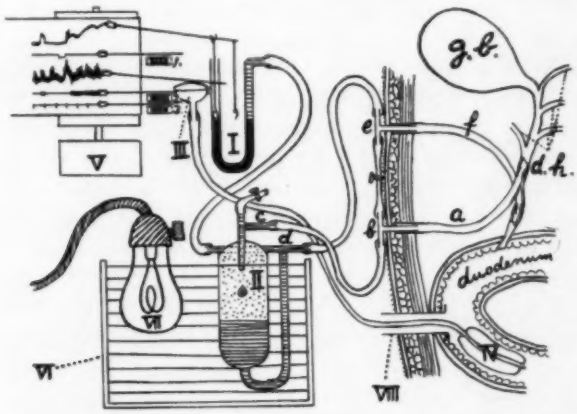

Fig. 1.—The following designations are used: *g. b.*, gallbladder; *d. h.*, ductus hepaticus; *ab* and *fe*, intubated cannulas; *I*, mercury manometer; *II*, drop counter of bile; *III*, tambour; *IV*, rubber balloon in the duodenum; *V*, kymograph; *VIII*, duodenal fistula.

When the tubing between *e* and *b* is disconnected by a clamp, the bile from the upper part of the biliary tract (*g. b.* and *d. h.*), passing through *a*, *b*, *c*, *II*, *d*, *e* and *f*, is evacuated into the duodenum. The volume and time of evacuation of bile are measured by a drop counter (*II*) containing liquid paraffin. The intracholedochal pressure is traced with the U-shaped mercury manometer (*I*). The movements of the duodenum are traced by the tambour by air conduction from the duodenal balloon.

and 3 recordings of the changes in sphincteric resistance at the lower end of the common bile duct were added to the records.

PERIODIC TYPES OF ACTIVITY

Case 1.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 12 Kg. The observation was made on the eleventh day after operation, March 6, 1936. The experimental method is shown in figure 1. As

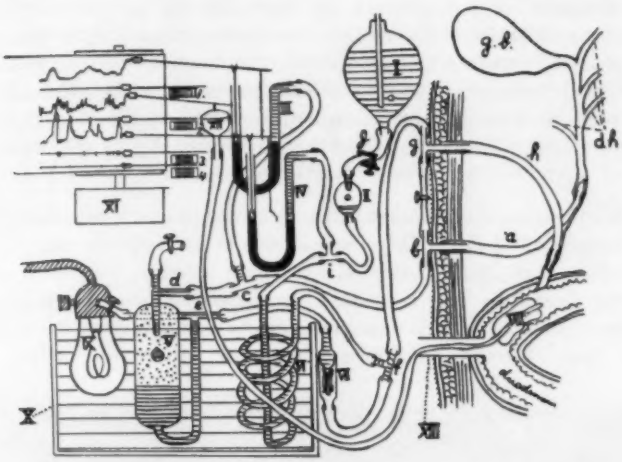

Fig. 2.—The following designations are used: *I*, flask containing Ringer's solution; *II*, drop regulator; *III* and *IV*, mercury manometers; *VI*, spiral glass tube; *VII*, William's valve, which prevents regurgitation of fluid.

In this, additions for the observation of pressure changes of the sphincteric mechanism are made to the apparatus in figure 1. The flask containing Ringer's solution is fixed at a height of 60 cm. or more, and the solution flows at a constant rate, passing through *II*, *i*, *VI*, *f*, *g*, *h* and the lower part of the choledochus into the duodenum. Therefore, when the pressure changes in this conduction system below *j* are traced by a manometer (*IV*), this would directly indicate the changes in tonus of the lower part of the choledochus. Regurgitation of Ringer's solution in the bile drop counter is prevented by a William's valve, so that when the pressure in the upper part of the duct overcomes the tonus of the sphincter of Oddi, the bile may be evacuated into the duodenum.

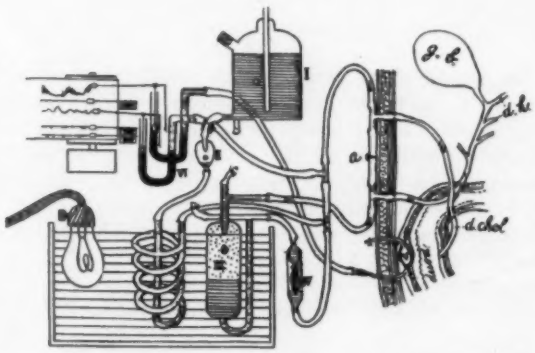

Fig. 3.—With this apparatus the movement of the duodenum was observed by a method in which a small balloon (*V*) was placed inside the duodenal wall. Otherwise this is the same as figure 2.

may be seen in figure 4, the duodenum showed periodic movements, and the curve is almost the same as that observed for man. During the resting phase of the duodenum the gallbladder continued to be relaxed and the intracholedochal pressure was only about 30 mm. of water, so that no bile was evacuated into the duodenum. When the duodenum moved, the intracholedochal pressure showed continuous and rhythmic rises of 80 to 120 mm. of water, according to the tonic and rhythmic contractions of the gallbladder. The bile was evacuated into the duodenum continuously or intermittently, corresponding to the peak of intracholedochal pressure.

Case 2.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 11.5 Kg. The observation was made on the thirty-fourth day after operation, May 23, 1936 (fig. 1). As may be seen in figure 5, the movements of the duodenum were periodic. The duodenum, after a resting period of ten minutes, passed into the active phase, at the end of which the tetanic form of activity was observed. Following this came the resting period, of thirty

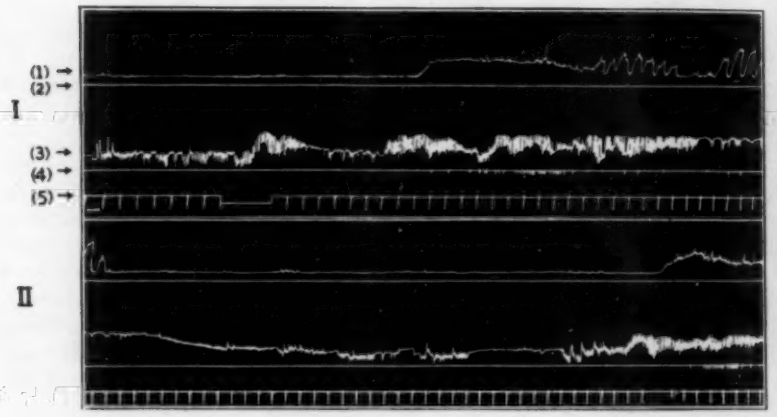

Fig. 4.—I and II are connecting. *1,* intracholedochal pressure; *2,* zero pressure line; *3,* duodenal movement; *4,* drop counts of bile evacuation into the duodenum; *5,* time (one minute).

minutes; then the second active period, which lasted for about seventy minutes, with another change to the tetanic type of movement. With regard to the evacuation of bile, corresponding to the active periods of the duodenum, there were also frequent spontaneous contractions of the gallbladder and an intermittent rise of the intracholedochal pressure, and, corresponding with this rise in pressure, intermittent evacuation of bile into the duodenum occurred.

Observations were carried out on the same dog the following day, with almost the same results.

Cases 3 and 4.—Investigations by the same methods showed almost similar results.

Case 5.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 11.5 Kg. The observation was made on the twenty-third day after operation, Nov. 11, 1936 (fig. 2). In this case a record of the changes in resistance at the distal end of the common bile duct was included in the obser-

vations. The outflow of bile and the duodenal movements were found to be the same as in cases 1 and 2. However, the resistance of the sphincter of Oddi during the active phase of the duodenum was 80 to 100 mm. of water pressure. The resistance frequently rose to 120 to 200 mm. of water pressure, and the waves of rising resistance apparently had no relation to the movements of the duodenum. At the beginning of the resting period the resistance was 120 mm., which gradually decreased to 80 mm. at the end of this period, and, moreover, no waves of changes in pressure were observed.

Cases 6 and 7.—The same methods (fig. 2) were used, with almost the same results. However, in case 6 during the active period the resistance of the sphincter of Oddi was 150 mm., with frequent waves of rises in resistance, reaching 180 to 270 mm. In the tetanic period the resistance appeared in several great waves, rising to 400 mm. and always corresponding to the rise of tonus in the duodenum.

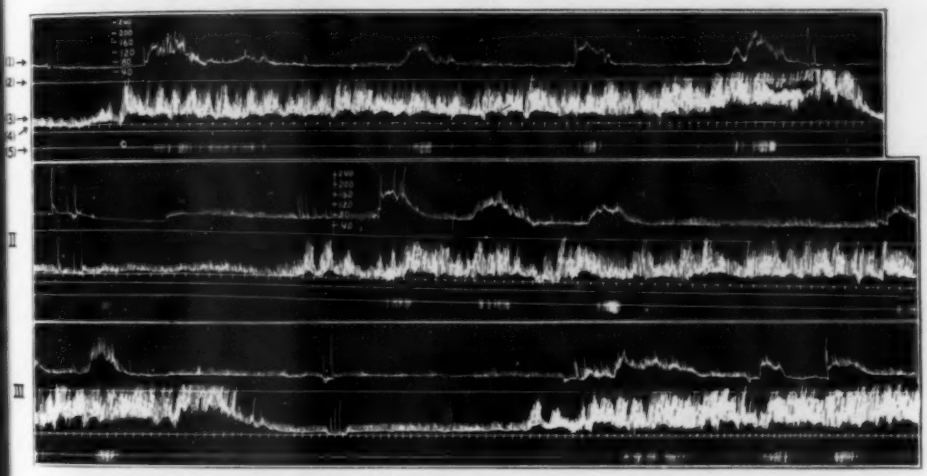

Fig. 5.—I, II and III are connecting. *1*, intracholedochal pressure; *2*, zero pressure line; *3*, duodenal movement; *4*, time (one minute); *5*, drops of bile evacuation into the duodenum.

With the passing of the duodenal movements into the resting phase, the resistance of the sphincter of Oddi decreased, not suddenly but gradually, from 240 mm. to 150 mm.

In case 7 the resistance of the sphincter of Oddi at the beginning of the experiment (resting period) was 100 mm. of water pressure. There was no evacuation of bile. With the change into the active period the resistance was generally 100 mm., although waves of rises reaching 160 mm. appeared now and again. When the intracholedochal pressure rose the sphincter of Oddi permitted evacuation of bile. However, in the tetanic period great waves of rising resistance (up to about 400 mm.) appeared, which checked the flow of bile.

Case 8.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the fourteenth day after operation, March 12, 1937 (fig. 3). In the previous cases it was observed that the discharge of bile into

the duodenum occurred concurrently with the rise of the intracholedochal pressure. In this case the changes in pressure at the distal end of the choledochus and the movements of the duodenum were recorded simultaneously. As may be seen in figure 6, from the first the duodenal movements increased gradually, and after eighty-five minutes tetanic movements appeared, lasting fifteen minutes and followed by a resting period of thirty minutes. Discharge of bile was seen during the active and tetanic periods but ceased in the resting period. The resistance at the sphincter of Oddi at the beginning of the active period was 200 to 240 mm., with intermittent variations reaching 280 to 320 mm. During the tetanic phase of the duodenum the resistance rose, with several high peaks (up to 500 mm.). These peaks were almost coincident with the variations in tonus and movements of the duodenum. During the resting phase of the duodenum the resistance curve showed a gradual decrease from 300 mm. at the beginning to 200 mm. at the end.

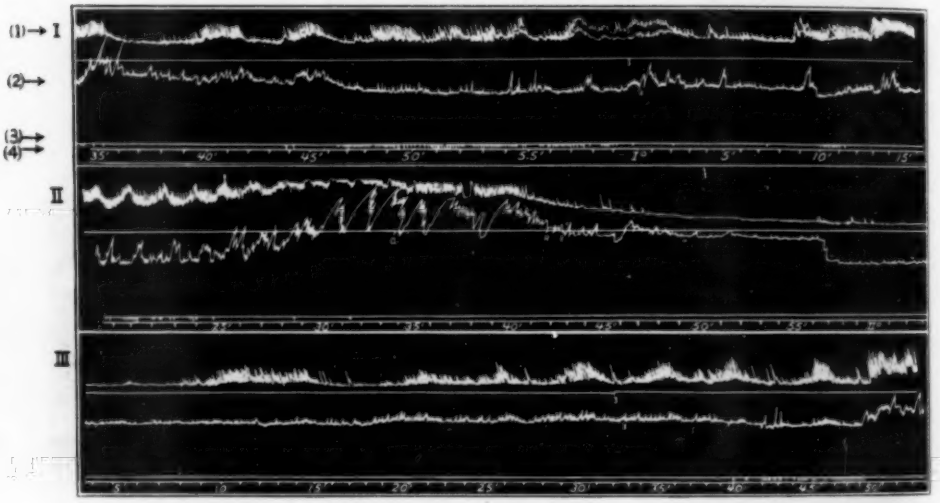

Fig. 6.—I, II and III are connecting. *1*, duodenal movements; *2*, changes in resistance of the distal part of the common duct; *3*, drops of bile evacuated; *4*, time (one minute).

NONPERIODIC TYPES OF ACTIVITY

Case 9.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the thirty-first day after operation, May 23, 1936 (fig. 1). As may be seen in figure 7, throughout the procedure no resting phase of the duodenum was seen. The intracholedochal pressure showed variations according to the rhythmic contractions of the gallbladder, and at the peak of the rise in pressure intermittent evacuation of bile occurred.

Cases 10 and 11.—The results obtained were almost the same as in case 9. In case 10 the intracholedochal pressure showed a minimum pressure of 60 to 80 mm. and irregular rises, reaching 100 to 120 mm., appeared intermittently, with evacuation of bile at the peak of each rise. In case 11 the minimum intracholedochal pressure was 70 mm., varying up to 190 mm., with evacuation of bile.

CASE 12.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the twenty-second day after operation, Dec. 1, 1936 (fig. 3). In this case records of the changes in pressure at the distal end of the choledochus were made. As is shown in figure 8, the movement of the duodenum was almost continuous, and the resistance at the distal end of the biliary tract

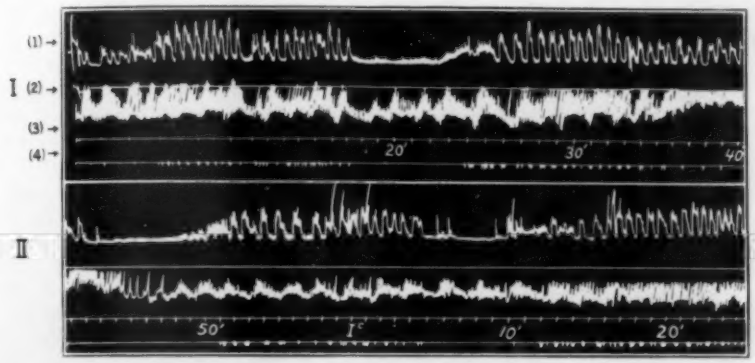

Fig. 7.—I and II are connecting. *1*, intracholedochal pressure; *2*, movements of the duodenum; *3*, time (one minute); *4*, bile evacuated into the duodenum.

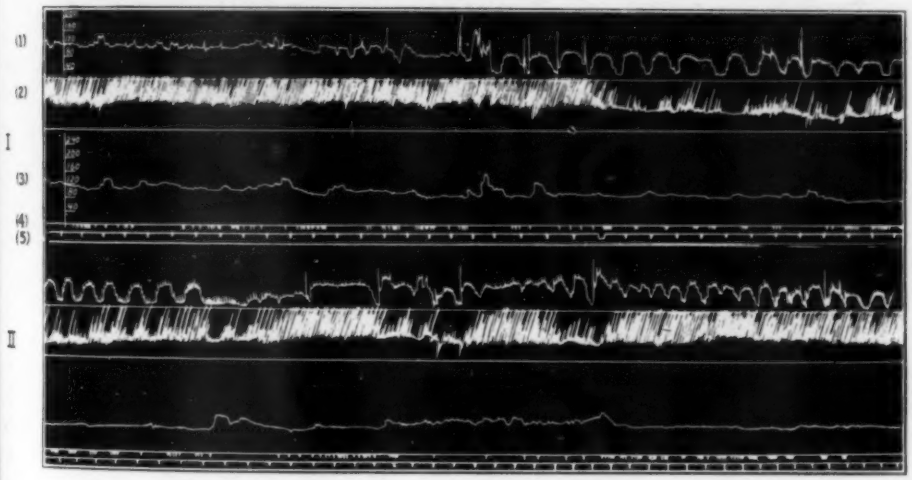

Fig. 8.—I and II are connecting. *1*, intracholedochal pressure; *2*, movements of the duodenum; *3*, changes in resistance at the distal part of the choledochus; *4*, drops of bile evacuated into the duodenum; *5*, time (one minute).

varied from about 80 mm. to 120 mm. of water pressure. The intracholedochal pressure showed also continuous or rhythmic movement, varying up to about 120 mm. Evacuation of bile took place with the rise in intracholedochal pressure.

This animal was observed again on the twenty-eighth day after operation. and almost the same results were obtained.

ABNORMAL TYPES OF ACTIVITY

CASE 13.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 12.7 Kg. The observation was made on the twenty-second day after operation, April 15, 1936 (fig. 1). Throughout the four hour period of observation the duodenum showed almost continued activity. The intracholedochal pressure showed rises reaching 200 to 300 mm., with continuous or rhythmic waves; that is, the gallbladder was in a state of restless contraction, notwithstanding the fact that there was no flow of bile into the duodenum.

CASE 14.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 13.9 Kg. The observation was made on the twenty-first day after operation, Dec. 23, 1936 (fig. 2). As may be seen in figure 9, the duodenum showed restless activity. The intracholedochal pressure also showed variability, reaching 280 to 320 mm., according to the uncertain contractions of the gallbladder. The resistance of the sphincter of Oddi rose to pressures of 320 to 450 mm., which checked the outflow of bile.

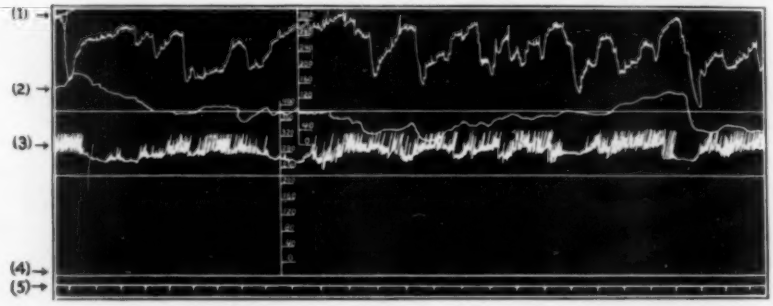

Fig. 9.—*1*, intracholedochal pressure; *2*, changes in resistance at the distal part of the choledochus; *3*, movements of the duodenum; *4*, bile evacuated into the duodenum; *5*, time (one minute).

SUMMARY

The investigations were carried out 16 times on 14 unanesthetized intubated dogs. In 8 cases a periodic relation between the duodenal movements and the evacuation of bile was seen. In 5 cases nonperiodic types of activity were seen, that is, continuous movement of the duodenum with an intermittent flow of bile. In 2 cases there was no evacuation of bile despite continued movement of the duodenum. The results obtained are almost the same as those of the previous investigations, conducted on man.

In the cases of the periodic type of duodenal movement, during the resting period the intracholedochal pressure showed a continuous decrease of about 30 to 80 mm. of water pressure, according to the relaxation of the gallbladder, and remained almost constant in each case, so that there was no evacuation of bile. During the active phase of the duodenum the intracholedochal pressure became intermittent,

with tonic or rhythmic rises in pressure corresponding to the spontaneous contractions of the gallbladder. At the peak of the tonic or rhythmic rises (120 to 200 mm.) bile flowed into the duodenum, the evacuation being intermittent. Regarding the flow of bile, it is difficult to say at which point in the period of duodenal activity the evacuation is greatest.

The resistance at the distal end of the common duct during the resting phase of the duodenum was 80 to 240 mm., without waves of variation in the pressure. That is, there was gradual decrease from the beginning of the resting period to the end of the period, or to the beginning of the active period. In case 6, starting at 240 mm., the pressure diminished gradually to 150 mm. at the end of the period. In case 8, at the beginning the resistance was about 300 mm., and it decreased gradually to 200 mm. at the end of the resting period.

The resistance during the active period remained about the same as that at the end of the resting period. However, there appeared waves of variation in pressure (120 to 270 mm.). These waves sometimes appeared to have no apparent relation to the tonus of the duodenum, although the contrary was also seen, so that the two relations are probably interchangeable.

When the movements of the duodenum became vigorous and entered the tetanic phase, the resistance at the distal end of the common duct rose with several high waves, reaching 200 to 500 mm. These waves were almost coincident with the variations in tonus and the movements of the duodenum. In the tetanic period evacuation of bile may occur when the waves of resistance are at the weakest.

With the nonperiodic types of duodenal movement the intracholedochal pressure when the gallbladder was relaxed was in some cases 60 to 80 mm. of water. In these cases the rhythmic or tonic pressure waves rose at intervals of ten to twenty minutes, reaching 120 to 160 mm. and varying from several minutes to one-half hour in duration. In other cases the pressure remained continuous, with almost no relaxation period, so that there was intermittent or almost continued evacuation of bile. The resistance at the distal end of the common duct was 80 to 150 mm., with occasional variations ranging from 120 to 300 mm., which might or might not be concurrent with the tonus and the duodenal movements.

With the abnormal types of activity, despite the almost continuous movements of the duodenum there was no evacuation of bile. In these cases the intracholedochal pressure was seen to be irregular, with great variations (200 to 300 mm.), according to the incessant contractions of the gallbladder, while the resistance at the distal end of the common duct appeared over 320 mm., with waves reaching 500 mm. of water pressure.

ANOMALY OF THE RIGHT INFERIOR LARYNGEAL NERVE

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Injury of the inferior, or recurrent, laryngeal nerve is a definite hazard when subtotal thyroidectomy is performed. Knowing the anatomic variations to which this nerve may be subject near the inferior pole of the thyroid gland, the surgeon is forearmed and may avoid wounding the nerve. Occasionally, notwithstanding consummate care, homolateral paralysis of the vocal cord will be found after completion of the operation. Some unexplained injuries may be accounted for by an anomalous derivation of the inferior laryngeal nerve.

Origin of the inferior laryngeal nerve from the cervical portion of the vagus nerve is uncommon. Recently, during the performance of subtotal thyroidectomy by one of us (Pemberton) the right inferior thyroid artery was ligated in the usual manner just proximal to its entrance into the thyroid gland. At this time the inferior laryngeal nerve was seen to arise from the vagus nerve (fig. 1) and to pass directly behind the internal jugular vein and common carotid artery and then pursue the usual course of the recurrent nerve. This is the fifth instance in which such an anomaly has been observed by the same operator; the first case has been previously reported.[1]

EMBRYOLOGIC CONSIDERATIONS

The explanation for the anomaly is found in the embryologic development of the primary aortic arches. Pertinent to the subject is the disposition of the fourth, fifth and sixth arches. It will be recalled that the fourth right arch forms the right subclavian artery as far as the source of its internal mammary branch, whereas the fourth left arch constitutes the arch of the aorta between the origin of the left common carotid artery and the termination of the ductus arteriosus. The fifth arches are but transitory and connect the ventral aorta with the dorsal

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1. Pemberton, J. deJ., and Beaver, M. G.: Anomaly of Right Recurrent Laryngeal Nerve, Surg., Gynec. & Obst. **54**:594-595 (March) 1932.

parts of the sixth pair of arches. True fifth arches are probably not always developed, but when they occur they become manifest later in embryonic development and are imperfect. In order to adhere strictly to existing nomenclature, the fifth pair will be included in the total number. Only the sixth right arch vanishes; the sixth left arch gives origin to the pulmonary arteries and forms the ductus arteriosus, the latter normally becoming impervious a few days after birth.

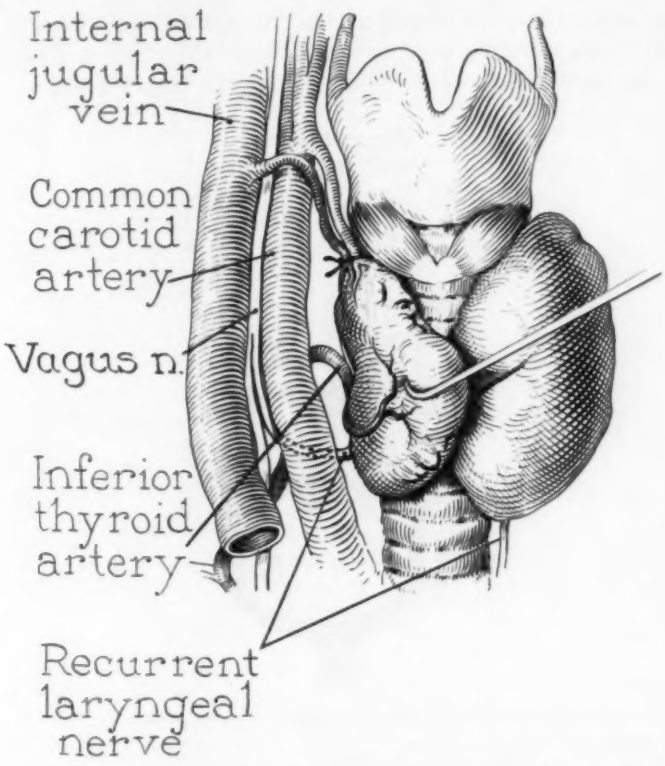

Fig. 1.—Anomalous origin of the right recurrent laryngeal nerve as found at operation.

It will further be recollected that the heart originally lies immediately behind the stomodeum but with elongation of the cervical region and development of the pulmonary apparatus recedes into the thorax. Consequently, the original position of the last three arches is considerably modified. On the right side the fourth arch is then found in the root of the neck, whereas on the left the fourth arch is within the thorax proper. If the transitory fifth arch is included among the primitive arches, the recurrent nerve thus passes under the sixth arch to the larynx. Because of this position the recurrent nerves are pulled caudally

as a result of the descent of the sixth pair of arches. Because of the disappearance of the fifth branchial arch on the left and of the fifth and sixth on the right, the left recurrent nerve proceeds around the obliterated ductus arteriosus, whereas the right encircles the fourth, or subclavian, arch (fig. 2). Thus, when the inferior laryngeal nerve is not found to be "recurrent," a correlative arterial anomaly involving the subclavian artery is also present. In 1899, Holzapfel [2] made an exhaustive review of such abnormally derived vessels. He reported that in 3 cases the inferior laryngeal nerve looped around the anomalously derived artery, whereas in 4 others the nerve passed around the right vertebral artery, which in these cases was a branch of the right common carotid

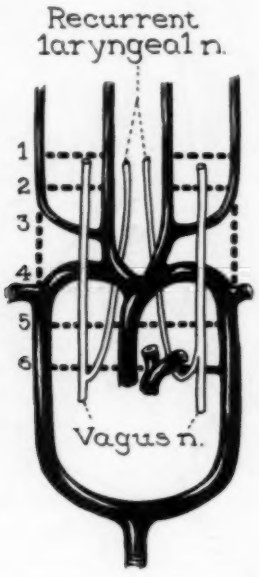

Fig. 2.—Normal relations between the primary aortic arches (*1, 2, 3, 4, 5* and *6*) and the recurrent laryngeal nerves.

artery. In the remaining 28 cases and in all others found by Williams [3] in the recent literature, the nerve is described as originating from the vagus at the level of the larynx and passing behind the right common carotid artery to its normal distribution.

Williams and others [4] have examined the aortic arch in 159 persons and have found an anomalous right subclavian artery in 4 instances

2. Holzapfel, G., cited by Williams.[3]

3. Williams, G. D.: Anomaly of the Inferior Laryngeal Nerve, Ann. Surg. **97**:828-830 (June) 1933.

4. Williams, G. D.; Aff, H. M.; Schmeckebier, M.; Edmonds, H. W., and Graul, E. G.: Variations in the Arrangement of the Branches Arising from the Aortic Arch in American Whites and Negroes, Anat. Rec. **54**:247-251 (Oct.) 1932.

(2.6 per cent). This figure is somewhat greater than those given by other authors, whose reported incidences are between 0.2 and 2 per cent.

ANATOMIC CONSIDERATIONS

With the foregoing embryologic facts in mind, the cervical derivation of the right inferior laryngeal nerve may be explained logically. Atrophy of the fifth and sixth arches on the right occurs normally. However, in the cases under consideration the right fourth arch, between the derivations of the common carotid and subclavian arteries, also vanishes. The inferior laryngeal nerve is not drawn caudally and will be found arising

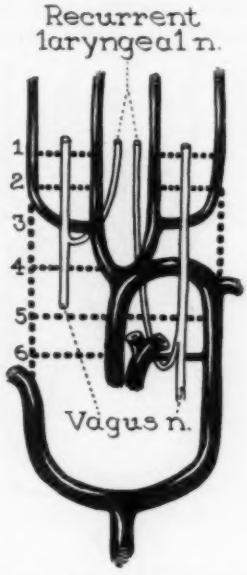

Fig. 3.—Origin of the inferior laryngeal nerve in the cervical region; *1, 2, 3, 4, 5* and *6*, primary aortic arches.

from the vagus nerve at the level of the larynx (fig. 3). Interesting, too, is the mode of origin of the subclavian artery in such cases. An innominate artery is lacking, and the great vessels arise from the aortic arch in the following order: right common carotid, left common carotid, left subclavian and right subclavian. The last vessel originates most commonly near the junction of the transverse and descending portions of the aorta (fig. 4). It then passes obliquely upward and to the right, anterior to the vertebrae and posterior to the trachea and esophagus, to the root of the neck. For blood to reach the right subclavian artery from the aorta it is necessary that it pass along that portion of the right fourth arch which intervenes between the origin of the subclavian artery

and the point at which the two aortic roots join to form the secondary trunk of the aorta. The right aortic root remains pervious, instead of disappearing as is usual. Consequently, the first portion of the anomalous right subclavian artery consists of a persistent right aortic root.

Variations of this circumstance (Piersol [5]), depending on the exact site and extent of the disappearing portion of the right fourth arch, may also modify the relation existing between the subclavian artery and its vertebral branch. The vertebral artery may arise from the subclavian artery, the aorta or even the common carotid artery. An explanation for the 4 cases of Holzapfel in which the right recurrent nerve passed around the vertebral artery is thus obtained. The vessel which is destined to be the common carotid is the artery of the third branchial

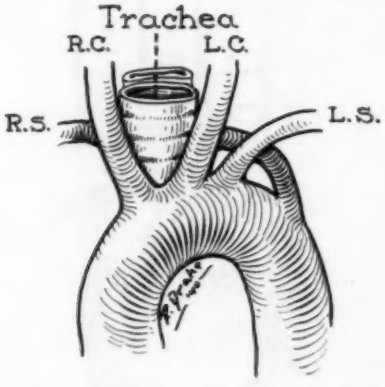

Fig. 4.—Anomalous origin of the right subclavian artery from the junction of the transverse and descending portions of the aorta.

arch. Since the right fourth, fifth and sixth arches have disappeared, the nerve passes around the third arch. Since the vertebral artery may be a branch of the carotid artery, the nerve must wind around both vessels, and thus it hooks around the vertebral artery.

A cervical origin of the left inferior laryngeal nerve is found much less frequently than is a like origin of the right inferior laryngeal nerve, because of the extremely complex relation that must exist to permit its occurrence. When the right fourth arch persists, the left fourth arch disappears and the aorta passes over the root of the right lung, that is, directly opposite to its usual course, the great vessels arising from the aorta are arranged in a manner opposite to that previously described. The left common carotid, the right common carotid, the right subclavian

5. Piersol, G. A.: Human Anatomy, ed. 9, Philadelphia, J. B. Lippincott Company, 1930.

and the left subclavian arteries arise in that order. This is not a true situs inversus viscerum but merely a reversal of the aortic arch and its branches. With atrophy of the fourth left arch between the derivations of the left common carotid and the left subclavian artery, the distal portion of the arch persists and forms the first portion of the subclavian artery. The process is an exact counterpart of the derivation of an anomalous subclavian artery on the right.

Variations of this anomaly concern principally the relations of the ductus arteriosus, or ligamentum arteriosum. It may unite with the descending aorta, in which case the ductus is derived from the right

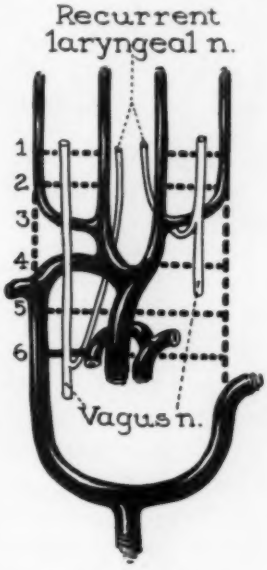

Fig. 5.—Origin of the inferior laryngeal nerve in the cervical region. This represents true transposition of the vessels and nerves as shown in figure 3; *1, 2, 3, 4, 5* and *6*, primary aortic arches.

sixth branchial vessel, or it may originate, as usual, from the left sixth branchial vessel, communicating with the left subclavian artery. When the ductus arteriosus is on the right and the left subclavian artery is found to arise from the descending aorta, the left inferior laryngeal nerve will not be drawn into the thorax, for the left fourth, fifth and sixth arches have vanished (fig. 5). If, however, the ductus arteriosus has its origin from the left sixth branchial vessel and communicates with the homolateral subclavian artery, the inferior laryngeal nerve will be found in the thorax.

If true transposition of the viscera is present, the ductus arteriosus will be formed from the right sixth branchial vessel. If, in addition to

this anomaly, the left fourth arch vanishes and the left subclavian artery is derived from the descending aorta, the inferior laryngeal nerve will arise in the neck, since the left fourth, fifth and sixth arches have disappeared and the nerve will not be drawn caudally.

SUMMARY

The practical surgical value of recognition of the occasional cervical origin of the "recurrent" laryngeal nerve is apparent. Blunt dissection lateral to the thyroid gland must be undertaken with care. In addition, if ligation of the inferior thyroid arteries external to the gland is contemplated, the vessels should be carefully isolated and visualized to avoid passing a ligature around the artery and the nerve together. In addition, an artery forceps must not be carelessly applied lateral to the thyroid gland, because of the danger of crushing the nerve. These accidents may explain a few of the heretofore unaccountable cases of paralysis of the vocal cords.

PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE

INVOLVEMENT OF THE ABDOMINAL WALL; REPORT OF AN UNUSUAL CASE

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Progressive bacterial synergistic gangrene is a chronic, rapidly spreading necrosis of the skin characterized by a distinct clinical picture and caused by a symbiosis of organisms, the cultural characteristics of which have been described by Meleney.[1] The disease is rare, although since 1924 an increasing number of case reports have appeared in current medical literature. Because of its infrequent occurrence it may not be recognized when first seen. The disease is so distressing to the patient and so persistent in its relentless destructive process that it is of the utmost importance that an early diagnosis be made and proper treatment instituted.

HISTORICAL CONSIDERATIONS

In 1909, Luckett[2] reported an unusual, rapidly spreading ulcer of the abdominal wall, which developed from a pimple. Removal of the scab, which followed picking of the pimple, revealed a small ulcer. Within six days this ulcer enlarged to 2 by 3 inches (5 by 7.6 cm.). Twelve days later it measured 5¼ by 10¼ inches (13.3 by 26 cm.) and had destroyed most of the skin covering the lower part of the abdomen. The usual local remedies were tried, but none of them were of any help in controlling the spread of the disease. Finally, the entire lesion, including a zone beyond the area of inflammation, was excised with the cautery. Complete and rapid recovery resulted.

Cullen[3] in 1924 described a "progressively enlarging ulcer of the abdominal wall involving the skin and fat, following drainage of an

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From the Department of Surgery, Northwestern University Medical School, and the Norwegian American Hospital.

1. Meleney, F. L.: Bacterial Synergism in Disease Processes, with a Confirmation of the Synergistic Bacterial Etiology of a Certain Type of Progressive Gangrene of the Abdominal Wall, Ann. Surg. **84**:961, 1931.

2. Luckett, W. H.: Large Phagedenic Ulcer of the Abdomen, Ann. Surg. **50**:605, 1909.

3. Cullen, T. S.: Progressively Enlarging Ulcer of Abdominal Wall Involving Skin and Fat Following Drainage of an Abdominal Abscess Apparently of Appendiceal Origin, Surg., Gynec. & Obst. **38**:579, 1924.

abdominal abscess apparently of appendiceal origin." In the same year Christopher [4] recorded his experiences with a "severe spreading carbuncular infection of the chest wall following rib resection."

In an interesting study, Bartlett [5] found that the older medical literature contains numerous accounts of enormous spreading ulcers of the skin, some of which appear to be identical with these lesions. The interest of modern surgeons, however, appears to date from the reports by Cullen and Christopher.

In 1926, Brewer and Meleney [6] reported a case similar to that reported by Cullen. Of special interest was the bacteriologic study, which pointed out the peculiar relation between the organisms concerned in the development of this disease. In 1931 Meleney [1] reported further studies confirming the synergistic bacterial causation of a certain type of progressive gangrene of the abdominal wall. These reports established the disease as a clinical entity and made possible an early accurate diagnosis.

In 1935, Stewart-Wallace [7] reported a case of gangrene of skin and subcutaneous fat following thoracotomy for drainage of an empyema similar to that in the case reported by Christopher. The gangrene progressed for eight months, at the end of which time it involved the back, from the occiput to the iliac crest, and the whole of the anterior abdominal surface. The patient died. In a recent report Vier [8] stated that a review of the literature at present reveals fewer than 40 authenticated case reports. One or more cases have been reported respectively from England, Japan, Sweden, Germany, Italy and Australia, although the vast majority have been reported from the United States. An extensive bibliography was given by Hirshfeld.[9]

CLINICAL PICTURE

Gangrene of the skin usually follows drainage of an abscess. The involved area becomes exceedingly tender, red and swollen. The wound

4. Christopher, F.: Severe Spreading Carbuncular Infection of Chest Wall Following Rib Resection Under Local Anesthesia, S. Clin. North America **4**: 795, 1924.

5. Bartlett, A. V.: Studies on Phagedenic Ulcers, Thesis, Yale University School of Medicine, 1938.

6. Brewer, G. C., and Meleney, F. L.: Progressive Gangrenous Infection of Skin and Subcutaneous Tissues Following Operation for Acute Perforative Appendicitis: A Study in Symbiosis, Ann. Surg. **84**:438, 1926.

7. Stewart-Wallace, A. M.: Progressive Post-Operative Gangrene of the Skin, Brit. J. Surg. **22**:642, 1935.

8. Vier, H. J.: Progressive Post-Operative Gangrene of the Abdominal Wall, Surgery **7**:334, 1940.

9. Hirshfeld, J. W.: Phagedenic Ulcer, Surgery **5**:894, 1939.

margins or the stitch holes become indurated, and the swollen area becomes purplish. Beyond this purple zone is a bright red zone, which passes into the normal skin. Within a few days the purplish areas widen and the part first affected becomes gangrenous. The color of the dead skin changes to a dirty grayish brown, and the surface is dull like suede leather. The purple zone spreads outward into the red, and as it does so the skin becomes raised above the normal level. The central side of the purple zone, toward the gangrene, is sharply defined but irregular and crenated. On the outer side it fades off into the red zone and flattens to the level of the normal skin. The gangrenous skin remains firmly adherent to the purple zone and becomes undermined at its free margin, but there is little if any undermining of the normal skin. As the process advances the gangrenous skin liquefies on its inner margin, leaving exposed a base of granulation tissue which gradually enlarges.

ETIOLOGY

The lesion is associated with a specific bacterial causation. This was clearly established by Brewer and Meleney [6] and confirmed in subsequent studies by Meleney [1] and Willard.[10] When careful anaerobic and aerobic methods of bacterial culture are employed, a micro-aerophilic non-hemolytic streptococcus [11] may be found in pure culture at the periphery of the lesion, not only in the red zone but occasionally just beyond it, in the relatively normal tissue. In the gangrenous tissue itself this streptococcus is associated with an aerobic hemolytic Staphylococcus aureus. That either organism alone is incapable of producing this lesion has been demonstrated. Pure cultures of either organism injected into animals result in no ulceration, but when the two organisms are combined in one-half the dose of each used separately a gangrenous process usually develops.

"The demonstration that these organisms can do something together which they cannot do alone suggests that the disease is the result of a synergistic action of the organisms, the non-hemolytic micro-aerophilic streptococcus being the essential organism in the zone of advance and in some way preparing the ground for the gangrenous action of the combined organisms. The streptococcus is most likely derived from the intestinal canal, while the staphylococcus may come from the patient's skin or from the air" (Meleney).

10. Willard, H. G.: Chronic Progressive Post-Operative Gangrene of the Abdominal Wall, Ann. Surg. **104**:227, 1936.

11. The micro-aerophilic streptococcus is one of a group which occurs frequently in the human intestine and in peritoneal exudates. It prefers an anaerobic environment and for the first cultivation must be obtained by anaerobic methods. However, after several transplantations on artificial mediums the organisms will grow on aerobic mediums as well.

DIFFERENTIAL DIAGNOSIS

Meleney [12] has called attention to the importance of making a prompt differential diagnosis between the various types of infectious gangrene of the skin, because the treatment of the different types varies markedly and early institution of the proper treatment not only may save life but will decrease the cicatrization and deformity. Four types of chronic gangrene of the skin due to infection have been described.

Progressive bacterial synergistic gangrene can be differentiated by its specific causation and its characteristic clinical picture. The absence of any constitutional disturbance except the effects of pain on the well-being of the patient and the presence of the local excruciating pain associated with the characteristic appearance of the ulcer make the clinical diagnosis evident. The demonstration of the hemolytic Staph. aureus in aerobic culture and of nonhemolytic streptococci when the latter can be grown in anaerobic culture establishes the specific nature of the disease. The uselessness of all forms of therapy other than complete excision, as far as the present status of this disease is concerned, is established.

Amebic infection with gangrene may follow the drainage of an amebic abscess of the liver. Amebas may be found in the stool but are numerous in the exudate of the wound and in the tissue. Specific therapy for amebiasis is indicated.

Gangrenous impetigo is usually associated with hemolytic streptococci and staphylococci. The lesions are usually multiple and may coalesce but are seldom large. Arising as vesicles, they soon pustulate and become gangrenous. Adequate treatment requires removal of crusts and intensive local application of ammoniated mercury ointment in addition to general nutritional treatment.

Fusospirochetal gangrene usually occurs in a wound contaminated with oral secretions, such as the bite of a human being. The essential organisms are fusiform bacilli, spirilla and spirochetes, often associated with nonhemolytic streptococci.

In only one of the four types of chronic infectious gangrene—progressive bacterial synergistic gangrene—is the micro-aerophilic nonhemolytic streptococcus present. Other conditions that must be differentiated are the chronic undermining ulcer and acute infectious gangrene.

The chronic undermining ulcer develops slowly, with liquefaction of the subcutaneous fat. The skin may take on a dull red or bluish appearance, thin out and develop a small opening, which enlarges until the margin fuses with the original ulcer. There is no gangrene of the skin with this type of ulceration. Moderate pain is present. The micro-aerophilic streptococcus can be grown from this lesion anaerobically. The use of zinc peroxide causes rapid healing of the process.

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12. Meleney, F. L.: A Differential Diagnosis Between Certain Types of Infectious Gangrene of the Skin, Surg., Gynec. & Obst. **56**:847, 1933.

The acute forms of infectious gangrene are differentiated by their rapid spread. In cases of gangrene due to the hemolytic streptococcus the onset is insidious. Redness and swelling followed by blister formation and the development of areas of gangrene within a week is characteristic. The gangrenous area is irregular, not sharply defined and associated with intense necrosis of the connective tissue. Bacteriologic examination shows a pure growth of streptococci.

Gangrene due to erysipelas starts usually with a chill and high fever. The area of redness is sharply defined and well localized. Acute infectious gangrene must be differentiated from this condition because of the need of prompt multiple incisions to lessen the tension and provide drainage of the area of gangrene due to the hemolytic streptococcus. In cases of erysipelas such radical treatment is not necessary.

Gas gangrene can be recognized by the gas formation in the tissues and the bacterial flora observed on anaerobic cultivation.

TREATMENT

Up to the present time neither local applications to the ulcer nor partial excision within the outer, red zone of the lesion has been found to be of value in the cure of this disease. Systemic treatment too has not been of any use in the cases so far reported. Complete excision of the lesion, including a zone of normal tissue about the periphery of the red zone, down to the deep fascia actually removes the disease. The application of zinc peroxide cream [13] to the wound after excision inhibits growth of anaerobic organisms that may be deposited in or may have remained in the wound. This is necessary, since organisms have been found in the normal tissues beyond the red zone. The covering of the defect with skin grafts after a clean granulating surface has been obtained makes early healing possible and diminishes scar tissue formation.

REPORT OF CASE

A man 50 years of age was operated on July 2, 1937, forty-eight hours after the onset of symptoms of acute appendicitis. The localization of pain and tenderness

13. Effective zinc peroxide depends on the ability of the powder to evolve oxygen gas when suspended in distilled water. This effective material must be applied to all parts of the wound as a creamy suspension, and evaporation must be prevented by sealing the whole dressing with petrolatum or zinc oxide ointment. The powder is sterilized in convenient quantities of 10 to 50 Gm. in glass tubes. The content of one or more tubes is then thoroughly mixed by means of a syringe with enough distilled water to give an even creamy suspension about the consistency of 40 per cent cream. Effective material will usually be found to swell somewhat in the water, so that it thickens, and more water may have to be added during the course of the dressing. A thick paste is undesirable, since it will not flow freely into the recesses of a wound.

in the rectum, indicating a pelvic location of the appendix, warranted the use of a right paramedian incision instead of the usual muscle-splitting incision. An acutely inflamed gangrenous appendix was removed after the abdominal wound had been carefully walled off. The abdominal wall was closed in layers and healed by primary union. Sutures in the skin were removed on the tenth postoperative day, and the patient was discharged from the hospital four days later (July 16). On the seventeenth postoperative day (July 19), while at home, the patient noted a "pimple" to the left of and above the umbilicus. During the next two weeks this took on the appearance of a carbuncle, enlarged rapidly and sloughed in its central portion, leaving an ulcer with a necrotic edge. The use of warm moist compresses, sterile dressings and dry heat locally did not relieve the intense pain associated with this lesion, nor did the lesion show any tendency to cease spreading. The patient returned to the hospital on August 4. Physical examination showed the essential pathologic process to be limited to the abdominal wall. A necrotic, ulcerated lesion was located about the umbilicus, but the umbilicus was not involved in the necrotizing process. The lesion measured approximately 7 x 10 cm. in its axes and was 2 cm. deep. The central zone was a granulating surface. The edge of the ulcer had an overhanging margin of necrotic skin, dark yellow-gray, beneath which there exuded a thick purulent discharge. This rim varied in width from 1 to 3 cm. and was bounded on its outer border by a dark purple zone 2 to 3 mm. in width, with a dentate appearance. Beyond this was a zone of redness 2 to 3 cm. in width, which faded into the normal skin. The scar of the recent abdominal wound was well healed, and the ulcer did not invade this scar. Toward the upper end of the scar, at the site of a previously healed suture puncture wound, there appeared a watery discharge, but it was undecided whether this came from the adjacent ulcer or from the fat beneath the scar of the healed wound. Direct smears from the lesion showed many gram-positive coccic forms and a few short chain streptococci. Cultures in broth on aerobic mediums showed few streptococci and numerous staphylococci.

It was thought that a communication existed between the depth of the original wound and the spreading ulcer and that hidden infection served to initiate and continue the periumbilical infectious process. On August 4, with the patient under ethylene-oxygen anesthesia, the entire necrotic zone of the ulcer was excised and the upper portion of the recent abdominal wound was incised. No communication was found between the ulcer and the depths of the healed wound. The watery discharge noted previously was scant and lay adjacent to the umbilicus, in a space which appeared to communicate with the ulcer. The granulating surface was well irrigated with hydrogen peroxide and covered with sterile dressings. Between August 5 and August 19 the ulcer continued to spread and the pain persisted in its former intensity. The latter had a detrimental effect on the patient's well-being, as it resulted in a depressed mental state. A variety of local applications were employed, without curative effect. Potassium permanganate irrigations and dressings, potent zinc peroxide in distilled water, diluted solution of sodium hypochlorite U. S. P. (Dakin's solution), moist boric acid compresses and dry heat successively failed to curb the spread of the ulcer, but the upper portion of the old wound, which had been incised, did not become involved in the ulcerative process. Ninety grains (5.8 Gm.) of sulfanilamide was given during thirty-six hours, but the cyanosis, acute distress and sudden weakness of the patient prompted discontinuance of this medication. Aerobic cultures made from the wound exudate on August 16 showed staphylococci. Anaerobic cultures made on August 19 showed small diplococci, streptococci and staphylococci. Further identification of the

organisms was not made. A study of the literature made it increasingly evident that this case (fig. 1) corresponded accurately with the picture of the disease entity described by Meleney and called by him "progressive bacterial synergistic gangrene." When this was realized, on August 19, two weeks after the patient's readmission to the hospital, he was reoperated on, with ethylene-oxygen anesthesia, and the whole lesion was excised. Cessation of all symptoms was evident soon after excision of the lesion. The excised tissue included an outer zone of normal skin 2 cm. beyond the red zone and extended down to the deep fascia. This wound was covered with a cream made of sterile potent zinc peroxide in distilled water and

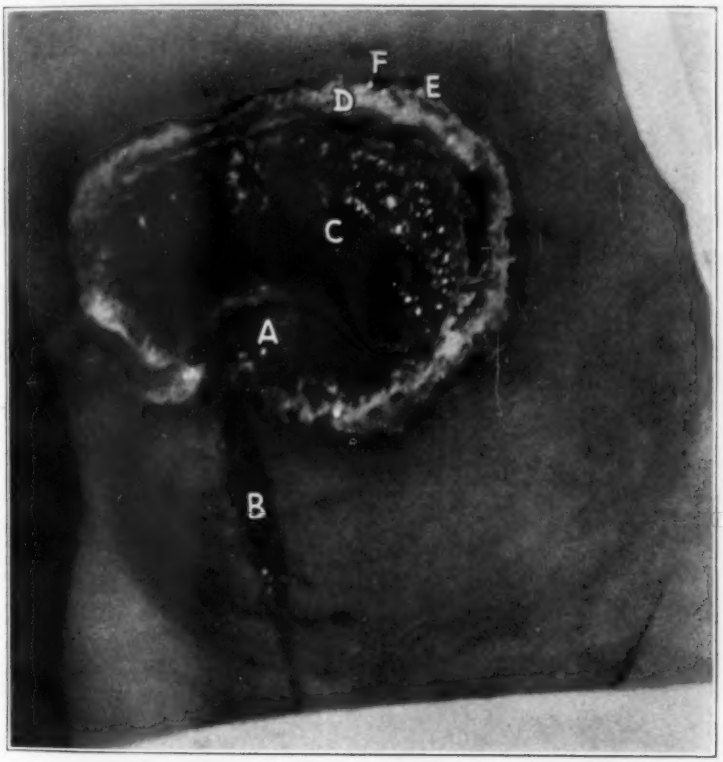

Fig. 1.—Progressive bacterial synergistic gangrene. *A*, umbilicus; *B*, incision into the original wound; *C*, granulating surface; *D*, necrotic zone; *E*, purple zone; *F*, elevated red zone.

was overlaid with sterile gauze saturated with the same material. Similar dressings were applied each day. A clean granulating surface developed, and twelve days after excision of the ulcer Thiersch grafts taken from the thigh under local anesthesia were placed along the periphery of the granulating wound. Because of personal circumstances the patient left the hospital on September 4. He was persuaded to return for complete skin grafting of the granulating surface. Intermediate thickness grafts were applied, but a sudden acute mental episode resulted

in dislocation of the dressings and sponges used for compression. Some of the grafts were lost, but healing eventually took place, with some scar formation on December 4. Recovery was complete (fig. 2).

COMMENT

This case illustrates several unusual features of this disease. The sequence of events points out the need for a prompt and thorough bacteriologic study to establish the identity of the disease early in its existence. While in most instances the disease has followed drainage of an

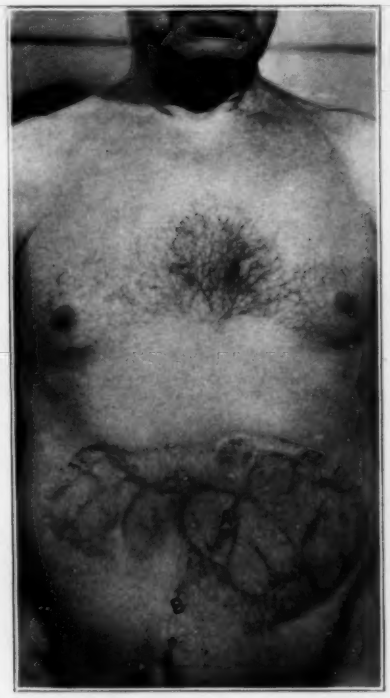

Fig. 2.—The healed wound. *A* and *B* have the same significance as in figure 1.

abscess, in the present instance no abscess was drained. The lesion arose independently of the incision in the abdominal wall, and despite its rapid spread it did not invade this incision. It is likely that tissue injury or tissue tension is necessary for establishment of the organism in the tissue. In many reported cases the disease developed about tension sutures. It is possible that the organisms associated with the disease may be present on the cutaneous surface and may enter the skin through some wound caused by a towel clip puncture wound, a scratch, an abrasion or a defect caused by removal of adhesive tape. While none of these could be

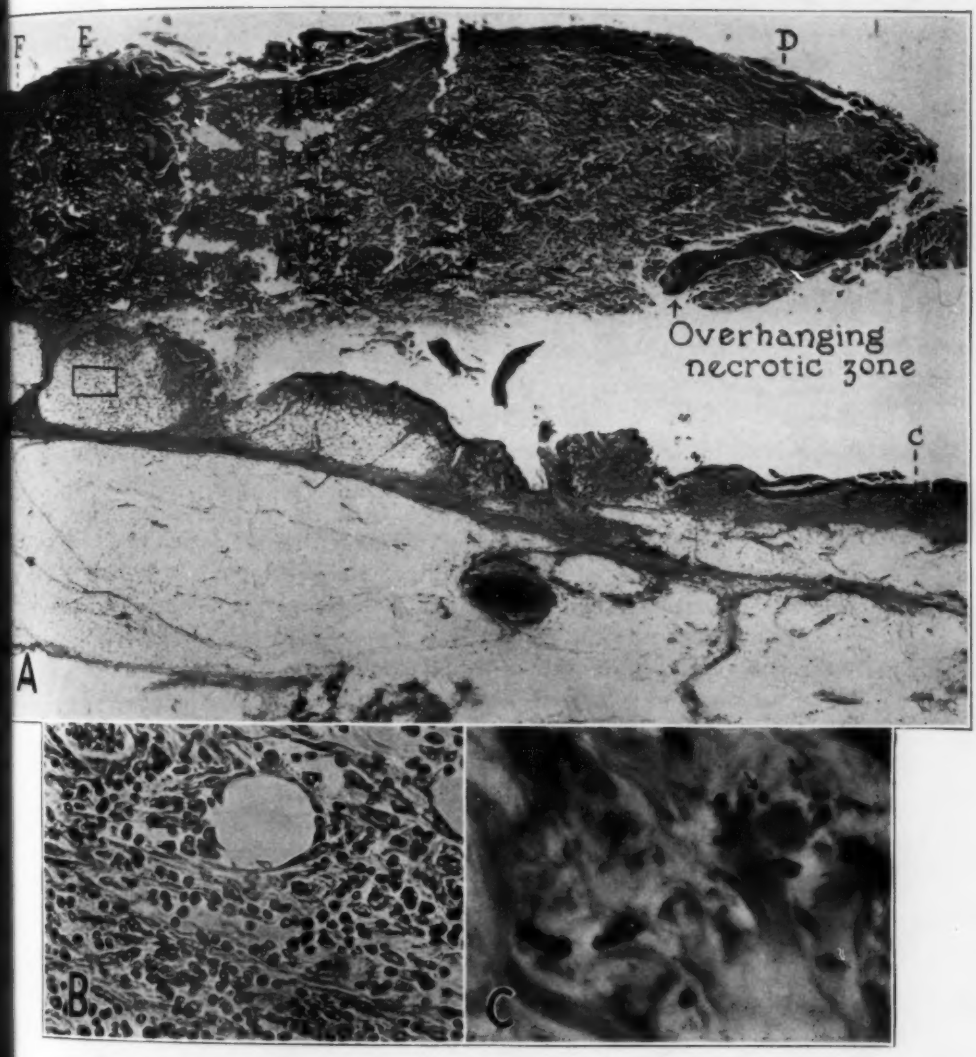

Fig. 3.—*A*, low power photomicrograph showing the margin of the ulcer composed of necrotic tissue. Note the infiltration (*D*) with large numbers of inflammatory cells. *B*, high power photomicrograph within the zone marked in *A*. The fat tissue is the site of dilated capillary blood vessels and large numbers of inflammatory cells. *C*, organisms stained with safranin in the red zone. These do not appear clearly in the photomicrograph, because the sections available for staining were too thick. When brought into accurate focus at different levels in the microscope, biscuit-shaped diplococci showed clearly.

established as having existed in the present instance, they remain as possibilities which should be avoided. The case parallels that reported by Luckett in 1909.

The reason for failure of all forms of therapy other than excision becomes obvious when it is realized that the organisms responsible for this disease are located deep in the tissues in the outer red zone. All applications which inhibit anaerobic bacterial growth fail to make contact with these organisms. Local excision of the necrotic zone alone fails to expose these organisms. The need for removal of a zone of normal tissue beyond the red zone is indicated by the finding of organisms here. A creamy suspension of potent zinc peroxide is necessary to flow freely into every exposed surface in order to destroy or inhibit the organisms that may still remain in the exposed wound surface.

PATHOLOGIC PICTURE

The gross appearance of the lesion is characteristic. Necrosis of the dermis appears to succeed destruction of the superficial layer of fat. In the present instance it is noteworthy that the umbilicus remained uninvolved throughout the course of the disease. The absence of fat in this area may account for its preservation. The old scar of the abdominal wound was not invaded by the organisms. It is likely that the scar tissue here prevented involvement of the subcutaneous fat by serving as a barrier to invasion. On microscopic section (fig. 3 *A*) the margin of the ulcer was seen to be composed of large numbers of polymorphonuclear leukocytes, chromatin debris and islands of swollen and edematous epidermis. The blood vessels in this area were dilated and engorged, and throughout were extravasations of red blood cells. The epidermis proper, which began about 2 cm. from the edge of the ulcer, was swollen, and the subepithelial tissue was the site of a dense accumulation of polymorphonuclear leukocytes which invaded and separated the bundles of elastic tissue. These infiltrations extended deep into the subcutis and were most marked about the blood vessels. In the deeper portions of the subcutaneous fat tissue were focal accumulations of polymorphonuclear leukocytes, lymphocytes and small round cells (fig. 3 *B*). Organisms could be seen (safranin stain) in the red zone (fig. 3 *C*). These appeared as diplococci. Meleney [12] has demonstrated large numbers of cocci in the red zone. These are well illustrated in his publications.

SUMMARY

A case of progressive bacterial synergistic gangrene is presented. Since the specific bacteriologic causation of this lesion has been conclusively demonstrated, an adequate bacteriologic study made early in the course of the disease would have been advantageous in establishing

the specific identity of the lesion. The publications of Meleney give in detail the interesting bacteriologic studies made of this disease. The appearance of the ulcer, with its margin of three zones, is characteristic. The present case differs from most other reported cases of the same disease in that the lesion did not commence at or involve the laparotomy wound or the sites where tension sutures were employed. The umbilicus, although completely encompassed, was not "consumed." The disease is a chronic specific ulceration associated with gangrene of the skin and must be differentiated from other types of chronic ulceration and other types of gangrene. Up to the present time recovery from this disease has been due in every instance to complete excision of the lesion, including a zone distal to the outer red margin. While the cautery has been recommended, excision by scalpel has proved satisfactory.

TREATMENT OF TUBERCULOSIS OF THE SHOULDER

A STUDY OF END RESULTS

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Some uncertainty exists as to the most suitable treatment for tuberculosis of the shoulder in adults. This is due partly to the relative rarity of this condition and partly to the inadequate follow-up after treatment. In the case of children the problem seems simpler, because there is almost complete agreement that treatment should be conservative. In this paper treatment will be evaluated on the basis of the experience at the Lakeville State Sanatorium.

Since tuberculosis is a systemic illness with local manifestations, the general treatment of the patient is of great importance. If possible, a period of sanatorium care should be instituted before operative procedures are undertaken. Fresh air, an adequate and balanced diet and regular rest periods are important in restoring the patient to his optimum physical condition. Immobilization of the affected shoulder in a plaster cast is orthodox therapy.

For children a long period of conservative treatment is imperative. By early operation the humeral epiphysis may be interfered with and the growth of the arm seriously impaired. Magnussen [1] treated 7 children conservatively by plaster immobilization and obtained a useful joint in every case.

Allard [2] recommended that a general anesthetic be administered if necessary and a plaster cast applied with the arm in abduction.

The conservative treatment per se is of limited value for adults. Graber-Duvernay [3] reported good results in 2 cases in which heliotherapy (in a revolving solarium) was combined with active motion. These results require confirmation and are in contradiction to the

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From the Massachusetts Department of Public Health and the Lakeville State Sanatorium.

1. Magnussen, R.: Seven Cases of Tuberculosis of the Shoulder in Children, Nord. med. tidskr. **10**:1420, 1935.

2. Allard, L.: L'ostéotomie sous-tubérositaire dans la scapulalgie de l'enfant, Rev. méd. franç. **16**:835-837 (Dec.) 1935.

3. Graber-Duvernay, J.: Deux observations de carie sèche de Volkmann. Résultats thérapeutiques, Bull. méd., Paris **48**:341-344 (May) 1934.

present teaching that the treatment of choice is immobilization, the ideal result being a solid ankylosis of the joint.

Except for incision and drainage, which are merely palliative, two types of corrective operative treatment have been employed, excision and arthrodesis. Steindler [4] recommended that arthrodesis be performed only when there is a chance of its working, that is, before there is too much melting down of tuberculous bone. He reserved resection for advanced conditions in which there is little expectation of obtaining a solid fusion. His best results were in his 5 cases of fusion.

Arthrodesis may be extra-articular, intra-articular or both. Putti [5] and Massart [6] have described the various technics in detail. The latter reported good results in 1 case fourteen months after the operation. In this case full thickness tibial grafts were used, together with small osteoperiosteal chips. Jones [7] recently described an extra-articular arthrodesis in which he angulated the acromion and implanted it in the humerus in the region of the greater tuberosity, thus securing ankylosis without actually encroaching on the diseased area. He obtained good functional and cosmetic results in 3 young adults followed eighteen months after operation. Curtis and Branch [8] employed the Jones technic in 2 children and found the operation well adapted for fusing a tuberculous joint in a child because it produces solid ankylosis without impairing the humeral epiphysis.

Codman [9] expressed the opinion that if a resection is undertaken radical excision of the articular head is preferable to excision of a localized area of diseased tissue. Richard and Courvoisier [10] advocated resection in preferance to arthrodesis because the diseased focus is removed and the resulting function better. They reported 5 cases. Meyer-Burgdorff [11] did an arthroplasty of the shoulder in 8 cases and obtained good results. In cases of advanced disease in which more

4. Steindler, A.: The Treatment of Tuberculosis of the Upper Extremity, Southwestern Med. **22**:168-171 (May) 1938.

5. Putti, V.: Artrodesi nella tuberculosi del ginocchio et della spalla, Chir. d. org. di movimento **18**:217-226 (Sept.) 1933.

6. Massart, R.: La tuberculose de l'épaule et l'artrodèse, Rev. de chir., Paris **68**:112-141, 1930.

7. Jones, R. W.: Extra-Articular Arthrodesis of the Shoulder, J. Bone & Joint Surg. **15**:862-871 (Oct.) 1933.

8. Curtis, F. E., and Branch, H. E.: Extra-Articular Arthrodesis of the Shoulder, J. Bone & Joint Surg. **19**:511-513 (April) 1937.

9. Codman, E. A.: The Shoulder, Boston, The Author, 1934, pp. 471-474.

10. Richard, A., and Courvoisier, J.: Indications et technique de la résection de l'épaule pour tumeur blanche, Presse méd. **41**:290-293 (Feb. 22) 1933.

11. Meyer-Burgdorff, H.: Die Resektion des Schultergelenkes bei Tuberkulose, Arch. f. klin. Chir. **175**:250-265, 1933.

conservative methods offer no hope, interscapulothoracic amputation of the arm can be done and a prosthetic appliance constructed for the patient. A case of such treatment was reported by Milch.[12]

Codman [9] pointed out that according to the present knowledge it is not possible to decide whether arthrodesis or excision is the superior operation. "We greatly need," he said, "a large collection of post-operative statistics to determine the relative value of these two operations." This paper represents a partial answer to that need.

The incidence of tuberculosis of the shoulder is probably less than 1 per cent of all cases of bone and joint tuberculosis. Sever [13] observed 17 cases in a study of 7,474 children with tuberculosis of the bones and joints. At the Lakeville State Sanatorium during the fourteen year period from 1926 to 1939 there were 24 cases of involvement of the shoulder among 1,076 admissions for tuberculosis of bones and joints, an incidence of 1.3 per cent. Of the 24 patients, 6 were female and 18 were male. The age on admission varied from 14 months to 57 years, with an average of 29 years. The age at onset of symptoms varied from 6 months to 49 years, with an average of 24 years. There were 5 cases of disease of the left shoulder and 19 cases of disease of the right. A follow-up study (largely by questionnaire) was obtained on every one of the 24 sanatorium patients included in this investigation.

Of the 24 patients studied, 12 underwent an arthrodesis (table 1); on 11 no operation was performed except occasional incision and drainage (table 2), and only 1 underwent excision of his shoulder joint. This last patient (J. C. C., fig. 1) was operated on at the Massachusetts General Hospital in 1919, and except for some limited motion he has "had no trouble since with the shoulder." He was treated at the Lakeville State Sanatorium primarily for tuberculosis of the hip, and a follow-up twenty-one years after his original operation revealed good function and no pain.

Of the 12 patients treated by arthrodesis, 4 were operated on at Lakeville, 6 at the Massachusetts General Hospital and 2 at the Newton Hospital. One of these (A. E. O.) is still hospitalized and has been followed for one year since operation. The remaining 11 were followed for three to thirteen years, or an average of seven years each, after operation. In every operative case the diagnosis of tuberculosis was confirmed pathologically. No patient required further operation or the continued use of any apparatus for support. At the time the follow-up study was made every patient reported some limitation of motion, but only 2 (E. W. B and A. J. C.) complained of pain. Function of the shoulder was good

12. Milch, H.: Interscapulo-Thoracic Amputation for Secondarily Infected Tuberculosis of Shoulder, Ann. Surg. **97**:381-386 (March) 1933.

13. Sever, J. W.: Tuberculosis of the Shoulder in Children, Boston M. & S. J. **162**:383-386, 1910.

TABLE 1.—*Patients Treated Operatively (by Arthrodesis)*

Initials	Age at Onset of Symptoms	Age on Admission to Lakeville State Sanatorium	Age at Operation	Sex	Side	Number of Sinuses on Admission	Tuberculosis of Other Organs	Place of Operation	Type of Operation	Years Followed Since Operation	End Results and Comment
M. W. B.	34	36	35	F	Right	3	0	Massachusetts General Hospital	Arthrodesis	11	Firm ankylosis; slight deformity; no sinuses; excellent function; working 5 years as bookkeeper (see fig. 5)
E. W. B.	32	34	34	M	Right	1	0	Massachusetts General Hospital	Arthrodesis with graft	7	Occasional "arthritic" pain; fair function; no sinuses
M. C.	32	33	33	M	Right	0	Wrist	Massachusetts General Hospital	Arthrodesis with graft	7	Good function; no pain
A. I. C.	17	26	26	M	Right	3	Lungs	Massachusetts General Hospital	Arthrodesis	3	Discharged at own request, against advice; sinuses drain constantly; some pain when drainage stops; has not worked; further operation contemplated
M. DeS.	31	32	32	M	Right	0	Lungs	Lakeville State Sanatorium	Arthrodesis with graft	4	Has worked as paper hanger since discharge; good function; no pain; limited motion
A. K.	4	6	7	M	Right	2	0	Lakeville State Sanatorium	Arthrodesis with graft	10	Excellent function; no pain; limited abduction; no sinuses or drainage
S. N.	39	40	39	M	Left	0	0	Massachusetts General Hospital	Arthrodesis	4	Discharged at own request, against advice; wearing plaster shoulder spica; working now; no pain; good function
L. P.	6	7	8	M	Right	0	0	Lakeville State Sanatorium	Arthrodesis with graft	13	Works repairing watches; no pain; good function; general health good
E. E. S.	7	10	10	M	Right	0	0	Newton Hospital	Arthrodesis	6	Good function; no pain
W. B. T.	20	20	20	M	Right	0	Foot	Newton Hospital	Arthrodesis with graft	7	Discharged at own request, against advice; slight shoulder stiffness and limited motion; good function; no pain
S. V.	45	46	46	M	Left	0	0	Massachusetts General Hospital	Arthrodesis with graft	7	Works as janitor since discharge; firm ankylosis; no pain; good function
A. E. O.	17	19	21	F	Right	0	Hip, Spine, Wrist, Lungs	Lakeville State Sanatorium	Arthrodesis	1	Still hospitalized; good ankylosis; wears an airplane splint; no pain

TABLE 2.—*Patients Treated Without Operation*

Initials	Age at Onset of Symptoms	Age on Admission to Lakeville State Sanatorium	Sex	Side	Number of Sinuses on Admission	Tuberculosis of Other Organs	Years Followed Since Discharge from Lakeville State Sanatorium	End Results and Comment
F. C.	49	57	M	Right	4	Spine	2	Discharged at own request, against advice; some pain; health failing; three sinuses still drain; weight loss 30 pounds (13.6 Kg.)
A. A. G.	17	29	F	Right	0	Foot, Wrist	5	Good function; slightly limited motion; health good; pregnant.
P. G.	41	42	M	Right	0	Lungs	6	Shoulder free from pain; good function; shoulder firmly ankylosed in 40 degree abduction (see fig. 4)
A. E. L.	39	41	M	Right	0	Spine, Testicle, Larynx, Lungs	1	Motion limited but free within limits; in sanatorium 6 months for pulmonary tuberculosis; required intubation for tuberculosis of larynx
J. J. L.	4	10	M	Right	0	Spine	3	Health fair; is able to play baseball; shoulder is ankylosed; good function
E. P.	23	25	F	Right	1	Spine	10	Able to work; no drainage; no reactivation of shoulder disease; good function; nephrectomy 5 years after discharge
A. S.	28	29	F	Right	2	Colon, Rectum	1	Died 3/28/33; shoulder disease spread; probably died from generalized tuberculosis
B. M. S.	25	27	F	Left	0	Chest, Tubes	1	Died 5/23/39; autopsy showed pulmonary tuberculosis and shoulder tuberculosis; thrombosis of left subclavicular and jugular veins; thoracoplasty 5/16/39
J. S. S.	8	24	M	Right	0	Kidneys, Hip	..	Died 12/2/38 of uremia and tuberculous nephritis; left nephrectomy on 2/14/34 and ureterostomy on 2/19/38
C. W.	39	41	M	Right	5	Glands, Hand	..	Died 2/15/34 of tuberculous shoulder; had downhill course; many sinus tracts (see fig. 3)
R. C.	½	1	M	Left	1	Chest	..	Hospitalized at Lakeville State Sanatorium past 6 years; wears plaster jacket with left shoulder spica; sinus not draining; no pain (see fig. 2)

or excellent in all but 1 (A. J. C.). He was the only patient too who continued to have draining sinuses, whereas 4 of the patients operated on had had draining sinuses on admission. Since the operations were done by different surgeons, there was no uniformity of technic. For 7 of the 12 patients, however, tibial or osteoperiosteal grafts were employed. It is interesting to note that only 5 of the 12 operatively treated patients had tuberculous involvement of other organs, whereas every one of the patients not operated on had multiple tuberculous foci.

Eleven patients were not operated on except for an occasional incision and drainage. In the cases of only 3 of this group was the diagnosis made pathologically; the condition of the remainder was

Fig. 1.—Left shoulder of J. C. C. seventeen years after excision. The patient reports good function and no pain.

diagnosed clinically and roentgenologically. One of the patients (R. C., fig. 2) is still in the hospital. Two patients died while in the sanatorium, 1 (J. S. S.) of uremia and tuberculous nephritis and the other of tuberculosis of the shoulder. The latter, a Chinese cook (C. W., fig. 3) had five draining sinuses and extensive involvement of his cervical glands. Two additional patients died about one year after discharge from the sanatorium, 1 (B. M. S.) of pulmonary tuberculosis and tuberculosis of the shoulder and the other of generalized tuberculosis. The latter (A. S) had been suffering from tuberculosis of the colon, rectum and peritoneum, and it appeared as if her shoulder disease had spread to involve the chest wall and the other shoulder as well.

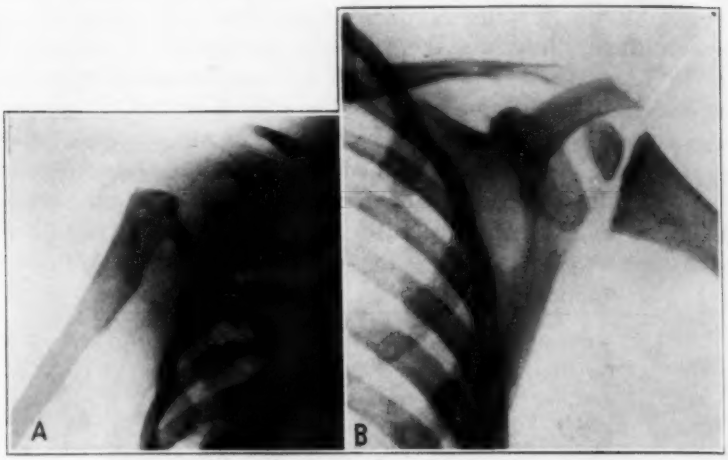

Fig. 2.—*A*, tuberculosis of the left shoulder in R. C., a 14 month old infant. There were drainage from one sinus and considerable pain. *B*, condition six years later. Note the development of the humeral head and the "squaring" of the epiphysis. The shoulder is still partly immobilized. There is no pain. The response to conservative treatment is favorable.

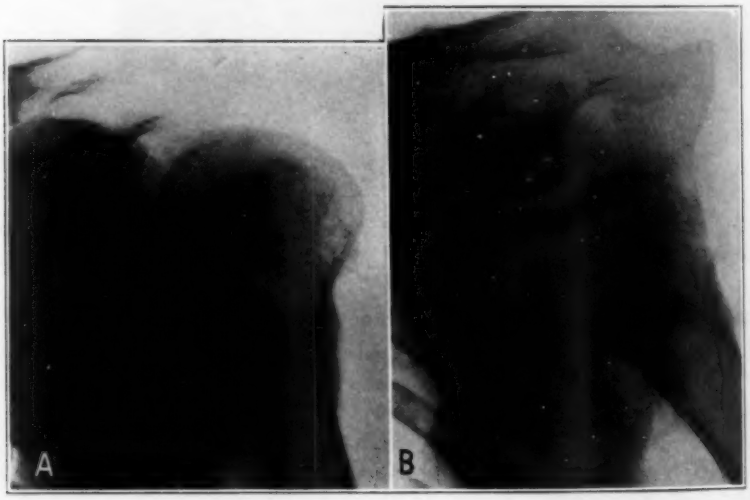

Fig. 3.—*A*, tuberculosis of the right shoulder in patient C. W. There is extensive destruction of the head of the humerus and the glenoid fossa. *B*, condition one year later; note the marked extension of the disease. The patient died. Operation in the presence of such a fulminating process would have been futile.

Fig. 4.—Tuberculosis of the right shoulder of patient P. G. Solid ankylosis was obtained in a nonoperative case. Good function is reported. Such firm bony union without operation is unusual.

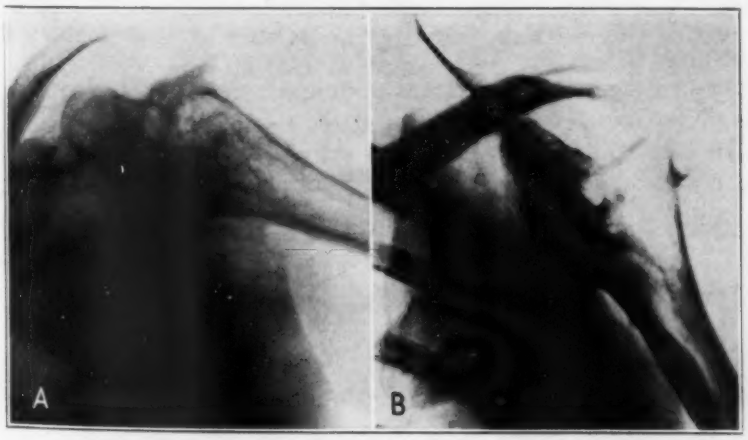

Fig. 5.—*A*, right shoulder of M. W. B. two years after arthrodesis. *B*, same shoulder nine years later; note the atrophy of the scapula and the maintenance of the scapulohumeral angle. The functional result is excellent.

The 6 remaining patients have been followed for one to ten years since discharge, an average of four years each. One (F. C) has lost weight and has three draining sinuses. Two others have only fair function, and the remaining 3 have good function and have shown no reactivation of the process.

CONCLUSIONS

The treatment of tuberculosis of the shoulder should consist of a period of sanatorium care followed by operation. Whether arthrodesis or excision should be performed is still an unsettled question, because the available statistics are too few to be decisive. Arthrodesis is a valuable operation. The 12 patients mentioned here on whom this operation was performed were followed for an average of seven years postoperatively and reported consistently good results. A single case in which an excision was done was followed for twenty-one years after operation, and the result in this isolated case is good. A period of observation before operation is important because it aids in evaluating the course of the tuberculous process and gives the patient an opportunity to improve his general condition. Needless to say, it is futile to operate in the presence of a rapidly fulminating disease or of marked toxicity from multiple tuberculous foci. With children, conservative treatment yields good results, but a well planned extra-articular fusion may shorten the duration of the illness and period of hospital care.

SUMMARY

The end results in 24 cases of tuberculosis of the shoulder are reported.

In 12 cases in which an arthrodesis was done the functional results were uniformly good.

In 11 cases no operation was performed; only 3 of the patients in this group reported good function of the shoulder.

In 1 case in which excision was done a functionally good shoulder was reported twenty-one years after operation.

RELATION OF THE SCALENUS ANTICUS MUSCLE TO PAIN IN THE SHOULDER

DIAGNOSTIC AND THERAPEUTIC VALUE OF PROCAINE INFILTRATION

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Pain in the region of the shoulder and arm is a frequent diagnostic and therapeutic problem. Such pain has often been attributed to some form of subacromial bursitis, of traumatic origin, of the chronic type with adhesions or of the acute or chronic type due to calcified deposits in the supraspinatus tendon, although the evidence in favor of the diagnosis was in many instances unconvincing. It was always difficult to understand the radiation of pain to the neck and down the arm as due to a bursal lesion, but Codman's observations so exactly fit the clinical picture that I was inclined to accept his explanation of a "pseudoneuritis." Codman,[1] in writing on calcified deposits in the supraspinatus tendon, said: "If there has been a long, painful stage all the adjoining nerves become sensitized and the phenomena we call 'neuritis' supervene." . . . "The pain or hyperesthesia, originally mainly felt in the circumflex distribution about the shoulder and near the insertion of the deltoid halfway down the arm, becomes more diffused. It shoots up into the neck, onto the back of the shoulder blade and down the distribution of the radial nerve to the thumb and forefinger. Even the ulnar and median nerves may become sensitized, the hand and fingers swell, and the skin over them becomes glossy. The picture is that of 'brachial neuritis' but removal of the calcified deposit relieves it."

The explanation of the phenomena observed in the hand and arm as due to a sensitization of adjoining nerves was difficult to follow, and in recent years I have become more and more impressed with the similarity of the clinical findings to those of the scalenus anticus syndrome. It has become apparent that pain in the shoulder produces spasm and contracture of the muscles of the shoulder girdle, in which the scalenus

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Read before the Philadelphia Academy of Surgery, May 6, 1940.

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1. Codman, E. A.: The Shoulder, Boston, The Author, 1934.

anticus often takes part, and thus a "secondary" scalenus anticus syndrome supervenes. That this is true may be proved by the prompt relief of the secondary symptoms by injection of procaine hydrochloride into the scalenus anticus muscle.

In the recent literature attention has also been focused on the role of the sympathetic nervous system in producing pain. There is no question that the pain of sprains and articular fractures may be relieved by local infiltration,[2] and there is evidence to indicate that block of the sympathetic fibers which supply an injured area produces a similar effect.[3] Block of the lumbar sympathetic fibers has been used by Ochsner and DeBakey [4] for relief of the pain and vascular stasis associated with thrombophlebitis. This newer concept of the origin of some types of pain I believe must be taken into account in considering pain in the region of the shoulder and I have some evidence to indicate that disturbance of the sympathetic nervous system has a part in the production of pain in this area.

THE SCALENUS ANTICUS SYNDROME

That the scalenus anticus muscle is a factor in producing the mechanical neuritis of the brachial plexus sometimes associated with a cervical rib has been known since 1906,[5] and section of the muscle for the relief of symptoms has been performed many times with good results, with or without removal of the cervical rib itself. There have been, however, a number of instances in which a typical cervical rib syndrome presented itself but in which no cervical rib could be demonstrated. Naffziger, in a personal communication to Ochsner, Gage and DeBakey,[6] described 2 cases in which relief was obtained by sectioning the scalenus anticus muscle. The latter authors reported 4 cases in which relief was obtained after such section and cited a report by Carroll of a similar successful operation. Since then the operation has been performed many times.

MECHANISM

The scalenus anticus muscle has its origin from the transverse processes of the third to the sixth cervical vertebra and its insertion into the scalene tubercle on the upper surface of the first rib, close to

2. Cullumbine, H.: Treatment of Fractures by Local Anaesthesia, Lancet **2**:552-553 (Sept. 2) 1939.

3. Campbell, W. G.: Role of Sympathetic Nervous System in Segmental Pain, Lancet **2**:930-932 (Oct. 28) 1939.

4. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics, Surgery **5**:491-497 (April) 1939.

5. Naffziger, H. C., and Grant, W. T.: Neuritis of the Brachial Plexus Mechanical in Origin, Surg., Gynec. & Obst. **67**:722-730 (Dec.) 1938.

6. Ochsner, A.; Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, Am. J. Surg. **3**:669-693 (June) 1935.

the sternum. The brachial plexus and the subclavian artery lie behind the lower portion of the muscle and on the other scalenus muscles, in a triangular space made by the first rib below and the converging muscles above. There are sympathetic fibers lying on the under surface of the inner cord of the brachial plexus and on the prevertebral muscle mass.

Spasm, increased tension or unusual hypertrophy of the scalenus anticus muscle may cause direct pressure on the brachial plexus or may cause indirect pressure by elevating the first rib unduly, the elevated rib pressing into the brachial plexus and the subclavian artery as they arch over it to go down the arm. In addition, since the scalenus anticus muscle is supplied by branches of the lower four cervical nerves, which form the brachial plexus, irritation of the plexus is thought to cause further scalenus spasm with increased pressure on the plexus and further elevation of the first rib, establishing a vicious cycle.[6]

When the shoulder girdle droops, the first rib becomes relatively higher than normal, and patients with droopy shoulders are more likely to exhibit symptoms. This is borne out clinically.

This mechanical neuritis of the brachial plexus, with or without associated vascular disturbances, is manifested commonly by pain about the shoulder; however, the pain may be located anywhere from the neck to the fingers. It is occasionally accompanied with tingling and numbness along the inner side of the arm, along the forearm and in the fourth and fifth fingers. Vascular disturbances may be present, such as diminished or absent radial pulse, coldness and cyanosis of the arm and hand.

ETIOLOGY

Naffziger and Grant [5] have pointed out that the relative position of the shoulder is high in infants and children and that a gradual descent occurs to the adult position; in the female the descent is greater and the ultimate position of the shoulder is more sloping. He suggested also that the loss of muscular tone and the drooping of the shoulders seen in the aged may be additional factors.

The inciting cause of the syndrome has so far not been clear. The majority of patients have given a history of some minor injury to the shoulder, so that possibly a sprain of the scalenus anticus muscle may have occurred. In the cases of others who recalled no injury, it has been assumed that the progressive dropping of the shoulder with advancing years was the only factor. In 1938 Freiberg [7] expressed the opinion that spasm of the scalenus anticus muscle might be a complication of many common lesions about the shoulder girdle, such as calcification

7. Freiberg, J. A.: The Scalenus Anterior Muscle in Relation to Shoulder and Arm Pain, J. Bone & Joint Surg. **4**:860-869 (Oct.) 1938.

of the supraspinatus tendon, arthritis of the shoulder or arthritis of the cervical portion of the spine, and Bishop,[8] of the same clinic, in 1939 described in detail 1 of 11 cases of "a rather typical scalenus anticus syndrome in which the condition was entirely relieved by treatment of the calcification of the supraspinatus tendon." I hope to demonstrate that any painful lesion about the shoulder may excite spasm of the scalenus anticus muscle with its characteristic train of symptoms.

DIAGNOSIS

Ochsner, Gage and DeBakey tried to differentiate the scalenus anticus syndrome from similar clinical conditions, such as cervical rib, subacromial bursitis, rupture of the supraspinatus tendon, cervicodorsal sympathalgia, Raynaud's disease and brachial neuritis. If, however, spasm of the scalenus anticus muscle may be a complication of any of these conditions, it becomes important to evaluate the part of the primary condition and the part of the spasm rather than to insist on a differential diagnosis. These authors based the diagnosis of scalenus syndrome on (*a*) persistent localized tenderness over the scalenus anticus muscle in the supraclavicular space, with radiation of pain into the arm, and (*b*) vascular changes, "consisting of diminution in, and at times complete absence of the radial pulse produced by rotating the head toward the affected side and extending the chin," and oscillometrograms showing a definite decrease in the index on the affected side, both thought to be due to pressure on the subclavian artery.

Theis[9] studied these diagnostic criteria and came to these conclusions: 1. Since more than 50 per cent of the conditions diagnosed as scalenus anticus syndrome are associated with a history of trauma to the neck or shoulder, the tenderness and the aggravation of the peripheral pain by digital pressure could occur with traumatic neuritis or any type of neuritis.

2. Reduction or obliteration of the peripheral pulse on deep inspiration with the scalenus anticus muscle on tension (head turned to the affected side and hyperextended) occurs in most normal persons. Normal subjects often exhibit an increased oscillometric index on changing from the sitting to the recumbent position, although the increases exhibited by patients suspected of having the scalenus anticus syndrome are frequently greater. It would therefore appear that only limited significance may be attached to local signs and vascular disturbances unless they are striking.

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8. Bishop, W. A.: Calcification of the Supraspinatus Tendon, Arch. Surg. **39**:231-246 (Aug.) 1939.

9. Theis, F. V.: Scalenus Anticus Syndrome and Cervical Ribs, Surgery **6**:112-125 (July) 1939.

Gage,[10] in April 1939, suggested that one might get temporary relief of the scalenus spasm by injecting procaine hydrochloride into the muscle and that this would be of importance in identifying the syndrome. He gave injections to 2 patients with the scalenus anticus syndrome, with relief of symptoms for eight hours and four hours, respectively. He gave an injection also to a patient with a cervical rib with temporary complete relief of symptoms. He performed the diagnostic test as follows: "With the patient in the recumbent position, the head is turned toward the unaffected side. The scalenus anticus muscle is palpated behind and lateral to the sterno-mastoid muscle. With the index finger of the left hand palpating the lateral border of the scalenus anticus muscle, a needle is inserted into its lateral edge. The muscle is then infiltrated with 1 per cent novocain through its lower half, care being taken not to infiltrate the phrenic nerve or brachial plexus. Within five to ten minutes the scalenus anticus muscle is completely relaxed and the patient is temporarily relieved of symptoms."

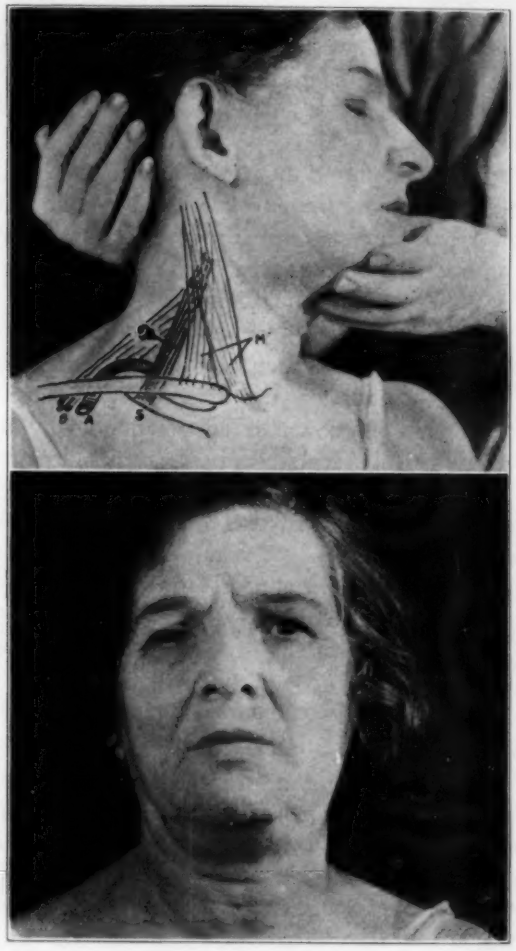
This seemed to be a simple method of determining the influence of the scalenus anticus muscle on the symptoms accompanying painful lesions of the shoulder of known or unknown cause. This procedure was carried out on 40 consecutive patients complaining of pain about the shoulder. The injections were made with the patient in the sitting position, about 10 cc. of 1 per cent procaine hydrochloride solution being used in most instances. A total of 78 injections was given. Usually the needle was pointed almost directly posteriorly, toward the transverse processes. Often contact with the processes was made, and the needle was then withdrawn slightly before the injection was started.

PHENOMENA OBSERVED AFTER INJECTION

The palpable thickness of the scalenus anticus muscle mass was variable, and in order to be certain of infiltrating the muscle thoroughly the needle was carried down close to the transverse processes of the cervical vertebrae, many times touching them. Before injection and several times during injection the plunger of the syringe was drawn back to determine whether the point of the needle was in a blood vessel. When blood was drawn the position of the needle was changed slightly. Relief of pain, when it occurred, usually began within two to five minutes, and the maximum effect was observed within ten to twenty minutes. Shortly after the relief of pain began, there were noticed in most cases redness and lacrimation of the eye on the side of injection, accompanied with enophthalmos, drooping of the eyelid and constriction of the pupil. The redness was due to intense dilatation of the subconjunctival vessels. In many instances the hand became warmer, flushed

10. Gage, M.: Scalenus Anticus Syndrome, Surgery **5**:599-601 (April) 1939.

and slightly larger than the one on the opposite side. These ocular and peripheral vascular phenomena were due to paralysis of the cervical sympathetic fibers and as a rule disappeared within forty-five to ninety minutes. Evidence of anesthesia of the brachial plexus was seen in only



The upper photograph was taken immediately after the injection and before withdrawal of the needle. The superimposed diagram shows the approximate relation of the important structures: *B*, brachial plexus (rather high); *A*, subclavian artery; *S*, insertion of the scalenus anticus muscle into the first rib; *M*, the sternal and clavicular heads of the sternocleidomastoid muscle. The lower photograph shows the drooping eyelid and enophthalmos after injection.

a few instances, consisting of some numbness in the fingers. In 1 instance there was numbness in the supraclavicular space. Occasionally the patient complained of slight giddiness, nausea and faintness, but in

no instance were these severe enough to cause concern. In 2 or 3 instances slight puffiness and discoloration at the base of the neck occurred, due to leakage from a perforated vein. Slight hoarseness was present in 2 or 3 patients after injection, and this disappeared in an hour or two. From 1 patient chyle was aspirated, probably from the thoracic duct at the point where it lies on the subclavian vein. No disturbance followed. No other untoward effects were observed.

CLASSIFICATION OF CONDITIONS

On reviewing the records I found that 34 of the patients could be classified into a few main groups, not always mutually exclusive, a point to be considered later. In 6 instances either the findings were inconclusive or the records were incomplete. The groups are as follows:

1. Scalenus syndrome..... 10
2. Scalenus syndrome following trauma..... 6
3. Subacromial bursitis with adhesions..... 12
4. Calcification in the supraspinatus tendon..... 3
5. Other conditions about the shoulder..... 3

1. *Scalenus Anticus Syndrome.*—The 10 cases placed in this group were characterized by the onset of pain in the brachial distribution without a history of antecedent trauma and by the absence of signs of subacromial bursitis or any other identifiable lesion of the neck or shoulder girdle. In 4 cases the symptoms were bilateral. Roentgen examination of the shoulder and of the cervical portion of the spine was indicated in about half of the cases and gave negative results in all but 1, in which there were unusually long transverse processes of the seventh cervical vertebra. Definite tenderness of the scalenus anticus muscle mass was present in 7 of the 14 shoulders.

The distribution of pain was variable, but in 7 of the 10 cases it was that distribution which is usually taken to characterize brachial neuritis —pain over the neck and shoulder radiating to the elbow or to the wrist and fingers. Pain over the scapula and the upper part of the chest may accompany the pain in the shoulder and arm or may be present without it.

The character of the pain varied considerably. It was described as dull, constant and nagging in some instances, as sharp and lancinating in others and in single cases as burning pain, a sense of tightness and a sensation as of pins and needles.

The duration of symptoms was less than two months in 2 cases and two months or over in 8 cases. As a rule the pain had become progressively worse from the time of onset to the time of the patient's admission to the hospital.

TABLE 1.—*Scalenus Syndrome*

Patient	Sex	Age	Duration of Symptoms	Distribution of Pain	Physical Findings	Result of Scalenus Injection	Progress
1. A. McC.	F	51	6 months	Dull over right scapula; occasional numbness right hand	Slight limitation of elevation and slight tenderness of right scalenus	6/12/39: Pain improved; motion easier; hand became numb	Did not return
2. E. V.	F	36	2 months	Burning pain right breast; sharp pain right shoulder, neck, scapula, ribs, breast and down arm	Tenderness over shoulder, right scalenus and trapezius; some spasm and limitation of elevation; lump in right breast	6/12/39: Pain very much relieved	6/16/39: Lump in breast excised for chronic cystic mastitis; 7/1/39: felt fine, discharged; 10/21/39: (follow-up) slight pain right breast and occasional slight stiffness of right arm
			Not stated	Outer side of left breast	Left scalenus tender; pressure on it caused pain in breast	10/21/39: Pain relieved	10/24/39: Complained of stiff neck and recurrence of pain
3. M. C.	F	36	3 months	Right side of neck; right deltoid, to elbow, wrist and fingers mainly index	Tender over scar distal to right acromion (lipoma removed 2 years before)	5/20/39: Pain completely relieved, index finger became numb	5/29/39: Complained of occasional pain on top of shoulder and slight pain in index finger; scalenus reinjection; 5/31/39: injection into painful scar; 7/24/39: slight recurrence, scalenus injection; 10/25/39: (follow-up) shoulder pain much inmproved; pain in hand and fingers completely gone
4. H. M. B.	M	34	2 months	Crampy; right shoulder, neck, between shoulders, along arm	Shoulder tender, pain when scalenus made tense	8/25/39: Fair relief of pain	9/1/39: No statement of recurrence; postural exercises prescribed
5. M. K.	M	66	11 days	Dull, constant, nagging, both shoulders, referred to insertion of deltoid	No abnormalities	11/10/39: Right side, immediate relief; 11/11/39: left side, immediate relief	Onset in hospital while recovering from operation for gastric carcinoma; no recurrence by 12/21/39 (discharged)
6. A. B.	F	41	Left, 6 months Right, 5 months	Left, slight, upper part of chest, shoulder and arm Right, severe, neck, shoulder, down arm	Old rheumatic heart disease; tender over insertion of right scalenus anticus; transverse processes of 7C vertebra unusually long on roentgen examination	12/19/39: Right side, no pain immediately prior to injection; scalenus injected and right 5-6-7 root injection; 12/22/39: left side, pain in upper left side of chest prior to injection; disappeared	12/22/39: Pain in right shoulder and neck definitely improved and pain in right arm absent since injection. 12/23/39: no recurrence of pain in arms; precordial pain less
7. J. Bo.	F	40	2 months	Left,tightness, numbness and occasional pins and needles sensation in whole shoulder, arm and side of chest; right, upper arm to hand; similar	Left scalenus more tender than right; pressure caused pain down arm; tender over head of left humerus	2/10/40: Left side, complete relief in 10 minutes; arm felt heavy	2/13/40: Recurrence; left reinjection, with complete immediate relief; complained of substernal oppression; no further injections
8. B. B.	F	22	3 weeks	Dull; right, neck and shoulder to wrist	Negative	4/12/40: Complete relief of pain; some numbness in supraclavicular space	4/18/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence: injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared
9. R. M.	M	58	5 months	Severe, right neck radiating to angle of jaw, occiput and back of shoulder	Aneurysm aorta and innominate; Horner's syndrome; syphilis of central nervous system	1/13/40: Complete relief for several hours	Reinjection 4 times with complete relief for a few hours each time; paravertebral alcohol injection, with slight relief
10. R. B.	F	45	2 months	Over shoulder, radiating to arm, forearm and hand	Right scalenus tender; pressure on it caused pain over shoulder; whole shoulder slightly tender	4/23/40: Not much pain prior to injection, but definite improvement in pain and mobility after injection	Pain returned in 1 hour; 4/25/40: reinjection with relief of pain and increased mobility; 4/30/40: slight pain only on complete abduction; full range of motion

9. R. M.	M	58	5 months	Severe, right neck radiating to angle of jaw, occiput and back of shoulder	Aneurysm aorta and innominate; Horner's syndrome; syphilis of central nervous system	1/13/40: Complete relief for several hours	Reinjection 4 times with complete relief for a few hours each time; paravertebral alcohol injection, with slight relief
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TABLE 2.—*Scalenus Anticus Syndrome Following Trauma*

Patient	Sex, Age	Date and Kind of Injury	Onset and Distribution of Pain	Physical Findings	Result of Scalenus Injection	Progress
1. E. W.	F, 60	12/14/39: Fell on face on pavement	Immediately after fall, then progressively worse; top of shoulder, radiating to elbow	Trapezius very tender, infraclavicular space tender	12/21/39: Immediate relief of all pain except in a small area behind middle of clavicle	12/22/39: Had first good night's sleep in a week; a little persistent pain over side of neck, insertion of deltoid and spine of scapula; reinjection, slight pain over spine of scapula remained
2. M. F.	F, 57	8/31/39: Lifted a baby abruptly; had noted paresthesias in left index and middle fingers for 2 years	Immediate; became worse, more at night, unable to sleep; top of left shoulder, deltoid, down medial side of arm	Motion painful; left scalenus very tender; transverse processes of 7th cervical vertebrae unusually long on roentgen examination	9/16/39: Marked immediate relief; no effect on paresthesias of fingers	Relief for 2 days; reinjection 9/19/39; relief for 3-4 days; reinjection 9/28/40; 10/17/39 (follow-up), slight pain; reinjection, 4/27/40, still some mild pain
3. A. P.	F, 54	1/15/40: Automobile accident	Immediate; severe, sharp; left side neck and left shoulder, radiating to elbow	Left scalenus and cervical transverse processes tender; tension on scalenus caused pain over shoulder, radiating down arm	1/22/40: Immediate but not complete relief of pain	Patient returned later; physical therapy given
4. J. P. M.	M, 40	1/15/40: Blow on left shoulder	Constant, aching, more severe anterior aspect left shoulder; radiating to neck and down arm to elbow	Tender over anterior aspect of left shoulder and over left scalenus; marked limitation of shoulder motion	1/19/40: Immediate relief of pain and muscle spasm; range of motion increased	Severe pain returned in 2 hours and lasted 2 hours; mild pain after 12 hours; no pain when examined on 1/20/40; 1/25/40, only slight pain at base of neck
5. J. B.	M, 36	11:30 p.m., 1/25/40: Fell downstairs and landed on right shoulder	Onset 6 a.m. 1/26 40; sharp pain in right shoulder, radiating up neck	Exquisite tenderness over acromion and trapezius, abduction of arm 40 degrees	1/26/40, 12 noon: Complete relief of pain at rest and only slight pain on motion; range of motion improved	1/27/40: Almost complete relief of pain and almost full range of motion; heat and methyl salicylate advised; 1/30/40, no pain; slight limitation of motion
6. H. S.	F, 40	4/1/40: Fell down steps and struck left shoulder	Steady aching pain over upper margin left scapula and lower portion of trapezius	Pain on full elevation of arm; left scalenus tender	4/9/39: About three fourths of pain disappeared; hand and arm became slightly numb	4/11/40: Complete relief of all pain and full range of motion

TABLE 3.—*Subacromial Bursitis with Adhesions*

Patient	Sex, Age	History	Distribution of Pain	Effect of Scalenus Injection	Progress
1. A. Z.	F, 68	Severe pain and restricted motion for 2 months; onset 1 month after a fall; treated by manipulation under anesthesia 5/12/39, followed by exercises; motion greatly improved, but pain persisted	Left shoulder, radiating over back and down arm to elbow	5/26/39: Immediate marked relief of pain	No recurrence by 7/7/39, when last seen
2. E. F.	F, 65	Severe pain and restricted motion for 1 year after straining shoulder; occasional prickly sensation in fingers; manipulation 3/6/39, followed by exercises; motion improved, but pain persisted	Right shoulder, base and back of neck	5/23/39: Immediate marked relief of pain	6/1/39: No recurrence, but pectoralis major was found tense and tender, procaine and saline solution injected; recurrence of pain 10/20/39, with occasional numbness in right 3d and 5th fingers; three additional injections by 2/13/40; last seen 3/1/40; pain slight, persistent myositis of pectoralis major (mild)
3. M. L.	F, 54	Severe pain and restricted motion following a strain of the shoulder 3 months before; occasional prickly sensation in fingers; manipulation 3/6/39; returned 10/17/39, little improved, having performed no exercises	Left shoulder, radiating down arm to fingers, which were cold, dusky and stiff	10/17/39: Immediate relief of pain; hand became warm, pink and less stiff	10/24/40: Partial recurrence of pain and vasomotor disturbance; had not been exercising; advised hospitalization; patient declined
4. C. S.	F, 61	Severe pain and restricted motion following a blow on the back of the shoulder 7 months before	Left shoulder down arm to wrist	12/8/39: Distinct relief of pain	Brachial plexus block anesthesia induced immediately after scalenus injection and manipulation; clavicle fractured; 12/9/39, pain at fracture site; no pain in shoulder or arm; 1/24/40, free of pain, range of motion much improved; discharged
5. A. T.	F, 44	Dull aching pain in right shoulder since automobile accident 9/13/40; fracture of both bones in right forearm; motion became restricted	Right shoulder, anterior, superior and posterior aspects	11/27/39: Immediate complete relief and increased range of motion	Relief lasted 2 or 3 days, then return of pain not so severe as before, exercises prescribed; 12/15/39, reinjection; no pain immediately before injection; range of motion improved
6. E. S.	F, 51	Fracture of right humerus 10/7/39; stiff shoulder 11/11/39; 11/16/39, complained of shoulder pain	Right acromioclavicular joint, radiating to insertion of deltoid	12/28/39: Pain over deltoid disappeared, but pain at acromioclavicular joint uninfluenced; pain on motion disappeared	Exercises prescribed; at a later visit pain was relieved and mobility much improved

6. E. S.	F, 51	Fracture of right humerus 10/7/39; stiff shoulder 11/11/39; 11/16/39, complained of shoulder pain	Right acromioclavicular joint, radiating to insertion of deltoid	appeared, but pain at acromioclavicular joint uninfluenced; pain on motion disappeared	pain was relieved and mobility much improved
7. A. K.	M, 53	While in bed recovering from an operation for peptic ulcer, began to have pain and restricted motion in both arms (5-6 weeks before); severe on right, mild on left	Right, top of shoulder down to 4th and 5th fingers; left, pain from deltoid to elbow	Right: 1/5/40, relief of pain and increased range of motion; left: 2/24/40, complete relief and increased mobility	1/6/40: Still improved; 1/8/40, injection; 1/11/40, manipulation; 1/18/40, recurrent severe pain, reinjection; 1/22/40, reinjection with relief for 2 days; recurrence; roentgen treatment, without relief; 2/24/40, pain still troublesome but not so severe
8. M. C. B.	F, 56	Progressively increasing pain and decreasing mobility, both shoulders, for 13 months; pain severe	Top of right shoulder, radiating to elbow; top of left shoulder, radiating to wrist	3/19/40: Right scalenus, little pain prior to injection	3/26/40: Stated that pain was less for 36 hours and then returned; admitted to hospital for traction in abduction, after which mobility increased; 4/23/40, left scalenus injection, pain diminished, mobility increased for 2 days; 4/30/40, right scalenus injection, mobility increased; patient much improved since admission
9. A. N.	F, 65	3/4/40: Fracture of right radius; 3/15/40,complained of soreness in left shoulder progressively worse since fall on shoulder 6 weeks before; 3/15/40, injection in tender area just lateral to coracoid, with relief of pain for 2 days; pain recurred; reinjection in this area on 2/19/40 with temporary relief	Left shoulder, soreness radiating to elbow; drawing and aching pain	4/12/40: No pain immediately prior to injection	4/15/40: Patient stated she had much more relief from the scalenus injection than from the other injections
10. D. R.	F, 62	12/16/39: Dull pain in right shoulder and inability to elevate arm following fall on hand 12/15/39; impacted fracture of head of humerus on roentgen examination	Right shoulder	12/16/39: No effect	
		3/15/40:Complained of progressively increasing pain and decreasing mobility in right shoulder	Right shoulder, radiating to forearm	3/15/40: Relief of pain and increased mobility	
11. M. G.	F, 51	Pain and restricted motion following a fall down stairs 2 months before; occasional numbness of fingers and swelling of hand	Top and back of right shoulder, radiating to fingers	2/21/40: Complete relief of pain, increased mobility	No recurrence of pain by 3/4/40, when she was sent to physical therapy department because of swelling and occasional numbness in right hand; 4/13/40 (follow-up), felt fine except for occasional slight pain
12. F. W.	M, 00	Severe pain and restricted motion for 7 months; roentgen therapy twice weekly for 2 months without benefit; physical therapy for 7 weeks without benefit	Dull, aching, constant; right shoulder, radiating to elbow	4/8/40: Immediate complete relief of pain; slight increase in mobility	No recurrence of pain by 4/9/40; shoulder manipulated under divinyl oxide, followed by pain from neck to wrist; scalenus injection, partial relief; 4/15/40: Still severe pain and restricted motion; injections in scalenus and subacromial bursa, and arm manipulated; 4/18/40, pain in bone, motion not improved; 4/29/40, pain only on motion, mobility much improved

The first injection of procaine hydrochloride into the scalenus muscle mass gave uniform and striking effects in these cases. In 13 shoulders there was either immediate complete relief of pain (8 cases) or marked amelioration (5 cases). In 1 shoulder there was little or no pain immediately prior to injection and hence no immediate change, but the customary pain which appeared afterward was much lessened.

The most surprising effect was the duration of relief. In several instances the pain failed to return. In others the relief lasted for many days and the recurrence was notably milder than the original pain. When this therapeutic effect became evident I was encouraged to repeat the injections in order to obtain permanent relief if possible. Four shoulders are known to be completely well or much improved, and 3 shoulders are improved and are still being treated. Seven patients have not returned for additional treatment, nor have I been able to obtain data on them by correspondence.

2. *Scalenus Anticus Syndrome Following Trauma.*—I have included in this group 6 cases in which the patients complained of pain about the shoulder following an injury, such as a fall, a blow or a strain. The duration of symptoms was six hours in 1 case and from four to sixteen days in 5 cases. The pain was a dull constant ache in some cases and was sharp and severe in the others. The pain was over the shoulder with radiation down the arm in 4 cases and over the shoulder and the side of the neck in 2 cases.

The physical signs in some cases were those of an acute soft tissue injury—tenderness over the scalenus and trapezius muscles and restriction of motion due to pain and muscle spasm. The signs in 1 patient suggested acute traumatic subacromial bursitis. In some the signs were meager, consisting only of tenderness over the scalenus muscles.

The first injection into the scalenus muscles gave immediate and complete or almost complete relief of pain in all cases, which lasted for one or more days. In 4 cases no additional injections were required. The recurrence in 1 patient was very mild and in the other was as severe as the original pain. This patient showed unusually long transverse processes of the seventh cervical vertebra, and she received additional injections, with considerable lasting relief.

An effect which I did not at first appreciate and record was the increased range of shoulder motion which followed injection. This was striking in several of the patients.

3. *Subacromial Bursitis with Adhesions.*—In this group I have placed the cases of 12 patients who complained of progressively increasing pain about the shoulder and who exhibited marked restriction of motion at the shoulder due to adhesions in the subacromial bursa. In 9 of these cases there was a history of trauma to the shoulder. The

symptoms were bilateral in 2 patients. The distribution of pain in 10 instances was over the shoulder, radiating down the arm, elbow, wrist or hand. In 3 instances the pain was limited to the shoulder and the base of the neck, and in 1 instance it was in the area extending from the deltoid to the elbow. In most patients the pain was extremely severe. It was often dull and aching but sometimes sharp, and it was intensely aggravated by motion, especially attempts to increase the limited mobility. The duration of symptoms was usually many months.

I have ordinarily treated subacromial bursitis with adhesions by manipulation (with general or local anesthesia) to separate the adhesions, followed by a program of exercises, such as wall climbing or swinging the arm in a stooping position or both. Large amounts of sedatives were usually necessary to control pain, and sometimes the pain persisted over long periods despite improvement in the range of motion. The first 2 patients in this group received the injections into the scalenus anticus muscle in an attempt to determine the cause of this severe and persistent pain. In 1 patient (A. Z.) there was immediate marked relief of pain, without recurrence by the time of discharge six weeks later. In the other patient (E. F.) there was no recurrence for five months. She was then given three additional injections, with satisfactory relief. The third patient (M. L.), who refused to exercise after manipulation, had intense pain and vasomotor phenomena associated with the bursal lesion. She exhibited a striking immediate response to injection, by relief of both pain and vascular spasm, partial relief being present even after one week. The fourth patient had severe pain and extremely dense adhesions; the injection gave distinct relief of pain. After twenty minutes block anesthesia of the brachial plexus was induced and she was manipulated. The clavicle was fractured in the course of manipulation. Although she complained of no recurrence of pain in the shoulder or arm at any time before discharge, it is likely that some slight pain was overshadowed by the pain of the fractured clavicle.

Two patients (A. K. and F. W.) were treated by manipulation with anesthesia, exercises and repeated injections into the scalenus anticus muscle, and I think that the injections resulted in considerably earlier relief of pain than would have been obtained otherwise.

Six patients exhibited a somewhat milder form of the condition, mainly in that the restriction of motion was not so extreme as in the severe forms. They were treated by exercises supplemented by repeated injections. Considerable improvement followed in each instance. One patient with bilateral extremely dense adhesions was treated by continuous traction in abduction for several days. The range of motion increased, but pain persisted. Exercises and additional injections into the scalenus anticus muscles resulted in considerable improvement.

One patient (D. R.) deserves particular comment. She came in complaining of dull pain in the shoulder and inability to elevate the arm, following a fall on the hand on the previous day. Injection had no effect on the pain, and roentgen examination disclosed a fracture of the head of the humerus, which was treated, with a good result. Three months later she complained of increasing pain and decreasing mobility in this shoulder. At this time injection relieved the pain and increased the mobility.

Every patient in this group experienced considerable relief of the constant pain immediately after injection, except for 2 who had little pain immediately prior to injection, and in these 2 the customary pain which appeared later was ameliorated for several days. Accompanying the relief of pain there was a definite increase in the mobility of the shoulder in most of the patients. The duration of relief was from several days to several months, in most instances varying with the progress of the bursitis. In those instances in which the adhesions had been separated by manipulation or exercises or both the relief often lasted for some time.

4. *Calcification in the Supraspinatus Tendon.*—Three patients presented themselves with severe pain in the shoulder due to calcification in the supraspinatus tendon. Two were in the acute phase of the condition and 1 in a subacute phase. The physical findings were typical—spasm of the shoulder muscles with severe pain on attempted motion and acute tenderness over the greater tuberosity. Only 1 patient exhibited tenderness over the scalenus anticus muscles.

Injection of procaine hydrochloride into the scalenus anticus muscle gave immediate relief of pain in all cases, accompanied with an increase in the range of motion. That the calcified area was not affected by the injection was evident from the residual limitation of motion in all cases and from the recorded persistence of the acute tenderness in 1 case. After the injection into the scalenus anticus muscle the patients were treated by injection of procaine hydrochloride into the calcified areas, with complete relief in the 2 cases of acute involvement and considerable improvement in the case in which the condition was subacute.

5. *Other Conditions Causing Pain in the Shoulder (Unresponsive to Injection).*—Two patients in this group suffered from narrowing of the intervertebral foramens and irritation of the roots of the brachial plexus, manifested in 1 case by intractable pain and in the other by paresthesias. Neither patient exhibited any response to injection. The third patient suffered from tendinitis of the long head of the biceps tendon in the bicipital groove. He also showed no response to injection into the scalenus anticus muscle but gave a striking response to injection of procaine hydrochloride into the peritendinous tissues. His original pain was well localized to the affected area.

Table 4.—*Calcification in the Supraspinatus Tendon*

TABLE 4.—*Calcification in the Supraspinatus Tendon*

Patient	Sex	Age	History	Physical Findings	Result of Scalenus Injection	Progress
1. H. C. W.	M	41	Pain in right shoulder, shooting down to fingers, progressively worse since onset 2 weeks before; severe while at rest, agonizing on motion	Rigid spasm of shoulder muscles; atrophy; acute tenderness at greater tuberosity; no scalene tenderness	1/29/40: Immediate relief of throbbing pain; hand became warmer; voluntary abduction increased from 10 to 45 degrees	After 25 minutes the bursa and supraspinatus tendon treated with injection of 15 cc. of 1% procaine hydrochloride; abduction increased to 135 degrees, with only slight pain; by 1/31/40 there was no pain, even on abduction to 135 degrees; exercises prescribed
2. S. G.	M	44	Pain in left shoulder radiating to elbow, continuous and severe; onset 6 months before	Spasm of shoulder muscles, tender over anterior aspect of shoulder; scalenus pressure caused shoulder pain; abduction 40 degrees	2/13/40: Relief of pain for half a day	2/15/40: Calcified area, injection and aspiration; 2/19/40, pain and mobility much improved; 3/5/40, mild recurrence, calcified area, injection; 3/11/40, scalenus injection for recurrent pain
			3/5/40: Complained of pain in right shoulder	Tender over greater tuberosity	No injection	Five roentgen treatments without improvement
3. G. V.	M	65	Severe throbbing pain over upper deltoid for 2 days; onset 1 hour after a strain	Spasm of shoulder muscles; acute tenderness of greater tuberosity and severe pain on motion; no scalene tenderness	4/25/40: Pain at rest disappeared entirely but still had pain on motion; abduction increased from 15 to 60 to 90 degrees; tenderness over greater tuberosity unchanged	4/26/40: Pain still much improved, abduction 30 degrees, calcified area injection; 4/29/40, very little pain, abduction 90 degrees, vastly improved

TABLE 5.—*Other Conditions Causing Pain in the Shoulder*

Diagnosis	Patient	Sex	Age	History	Findings	Result of Scalenus Injection	Progress
1. Narrowed intervertebral foramens	S. M.	F	74	Severe pain in left shoulder for 6 months; progressively worse; pain from below ear down to finger tips	Slight limitation of internal and external rotation; roentgen study of cervical spine showed encroachment on intervertebral foramens between C4 and C5 and between C5 and C6	6/12/39: No relief; repeated in 10 minutes; no relief	Four doses of thiamine chloride, 50 mg. each, by vein without benefit; subacromial bursa treated by injection of procaine hydrochloride; pain became worse; 5 roentgen treatments to cervical spine with trifling improvement
2. Narrowed intervertebral foramens	J. D.	M	63	Numbness and tingling in fingers of left hand for 2 years; pain in shoulder for a brief period at time of onset	Slight swelling of index finger and slight dulling of sensation in hand; cervical spine showed marked hypertrophic changes and encroachment on intervertebral foramens on the left from C2 to C6 and on the right from C3 to C5 on roentgen examination	2/8/40: Caused pain down arm; 2/13/40, no improvement	2/13/40: Patient thought there was slight improvement
3. Tendinitis of biceps	A. B.	M	21	Constant dull pain at right shoulder for 5 years; sharp pain on movement	Pain localized over deltoid distal to acromion; slight local tenderness; shoulder normal to roentgen examination	2/8/40: No spontaneous pain prior to injection, but had pain on motion; the latter not affected by the injection	2/13/40: Bicipital groove, 20 cc. of 1% procaine hydrochloride; relief for 3 days; repeated on 2/20/40; relief until 2/26/40, when he had only slight pain on motion

It may be noted here also that in patient D. R. (table 3) injection of the anesthetic into the scalenus anticus muscle produced no relief of the pain associated with a fracture of the humerus.

A brief mention of the 6 other patients in this series will complete the story of this experimental period. Five patients had very mild forms of subacromial bursitis interpreted as due to roughening of the bursa by villi bands or adhesions and had intermittent variable pain. They had practically no pain at the time of the test injection, and the later findings were inconclusive. One patient had ill defined dull pain of five years' duration, following a fall, with no limitation of motion and no roentgen abnormalities. The result of injection was inconclusive.

MECHANISM OF PAIN IN THE SHOULDER

Although scalenus spasm, hypertrophy or fibrosis may cause pain in the brachial distribution and vascular disturbances in the affected arm, my observations indicate that pain is present much more frequently than are vascular disturbances and that mild forms of the scalenus anticus syndrome may be overlooked if one depends on the usual criteria for diagnosis.

In the group of cases classified as examples of the scalenus anticus syndrome neither traumatic lesions nor other discoverable lesions about the shoulder girdle or neck were present. The patients were definitely characterized by droopy postures, which would suggest that the progressively lower position of the shoulder girdle caused progressively increased tension on the brachial plexus or increased angulation over the first rib, which finally caused pain. Reflex spasm of the scalenus anticus muscle may have followed the pain and in turn caused a definite progression of symptoms. It seems more likely, however, that some unaccustomed activity or position may have caused a myositis of the scalenus anticus muscle, which in turn precipitated symptoms in a subject made vulnerable by poor posture or by anatomic peculiarities.

Two patients (M. K. and A. K.), aged 66 years and 53 years respectively, had bilateral pain in the shoulder which came on while they were lying in bed recovering from an operation. The patient who was given an injection after eleven days of pain had permanent relief, while the other, who was not treated for six weeks, had adhesions in the subacromial bursa. The precipitating factor in both cases may have been prolonged stretching of the neck. Several patients associated the pain with prolonged use of the arm in writing, typing or doing housework, such as washing; again the possibility of primary myositis appears.

A stronger argument for primary myositis is my observation that permanent or prolonged relief follows injection of procaine hydrochloride. Myositic lesions elsewhere in the body often respond to this treatment.

In the group classified under "scalenus syndrome following trauma" I think that the lesion was an injury to the scalenus anticus muscle—traumatic myositis. The muscle goes into spasm just as does an injured dorsal muscle and causes symptoms by disturbing the brachial plexus. When the muscle spasm is abolished by injection of procaine hydrochloride the symptoms disappear, to return either in a much milder form or not at all. I have observed similar phenomena after treating muscular sprains of the back and fractures of the transverse processes of the lumbar vertebrae by injection.

The patients in the first two groups may be regarded as having a lesion primarily in the scalenus anticus muscle. Relief from this lesion resulted in relief of symptoms.

Those patients who suffered from subacromial bursitis with adhesions had a different situation. Bursitis with adhesions may follow an injury to the shoulder, such as fracture of the neck of the humerus or acute traumatic subacromial bursitis. These are associated with some hemorrhage and exudation about the subacromial bursa. If the arm is immobilized at the side for a sufficient length of time, the bursal surfaces agglutinate. When finally motion is attempted, traction on the adhesions causes pain and motion stays restricted. Spasm of the scalenus anticus muscle may be incited by the pain and may then cause the characteristic radiation down the arm.

It can be noted in table 3 that all but 1 of the patients were over 50 years of age. Meyer[11] has shown that attritional degenerative changes occur commonly in the supraspinatus tendon with advancing years. This results in roughening of the floor of the bursa. If atraumatic spasm of the scalenus anticus muscle or traumatic myositis is the initial lesion and causes pain and muscle spasm, the immobility may allow the roughened bursal surfaces to agglutinate and to become densely adherent. My observations suggest that this sequence of events occurs frequently. If one compares the patients in table 3 with those in table 2 one can observe that those in the group in table 3 were older and came in for treatment on the average four and one-half months after onset, while the group in table 2 came for treatment on the average seven days after onset. The latter group had already some limitation of motion, which in an elderly patient would finally result in bursal adhesions.

I have demonstrated by injection that a considerable element of spasm of the scalenus anticus muscle is present in these patients with bursal adhesions. If nothing was done to separate the adhesions they incited a recurrence of the spasm after a variable period, and the condition remained unchanged. When the adhesions were separated by

11. Meyer A. W.: Chronic Functional Lesions of Shoulder, Arch. Surg. **35:** 646-674 (Oct.) 1937.

manipulation and exercises or by exercises alone, the persistent pain due to scalenus spasm or fibrosis was substantially relieved by injection.

The intense pain experienced in the acute phase of calcification of the supraspinatus tendon is due in part to spasm of the scalenus anticus muscle. Injection afforded striking but limited relief. These observations parallel those of Bishop,[8] who described relief of the scalenus anticus syndrome after surgical removal of the deposits. In my cases the spasm did not recur after dispersal of the deposits by injection of procaine hydrochloride into the calcified area.

The patients in groups 3 and 4 may be regarded as having secondary lesions in the scalenus anticus muscle. Injection of procaine hydrochloride into this muscle identifies the lesion and relieves a great deal of the pain, which recurs after a short interval. Spasm of the scalenus anticus muscle usually continues until the primary bursal lesion has been disposed of and may continue much longer, owing probably to fibrosis in the muscle. After the primary lesion has been overcome, injection tends to give prolonged relief of the residual symptoms.

EFFECT ON THE SYMPATHETIC NERVOUS SYSTEM

With but few exceptions the injections were followed by striking ocular evidence of paralysis of the cervical sympathetic nerves. Less frequently there was vasodilatation in the arm. One cannot, therefore, exclude the possibility that the pain in many cases was due in part to a sympathetic reflex mechanism similar to that thought to be present after injuries elsewhere in the body and that interruption of these reflexes was responsible for the relief of pain. In favor of this view is the frequent presence of muscle atrophy in these patients. Against it is the very rare occurrence of vasospastic phenomena of marked degree, which were searched for in all the patients, as well as the observed duration of the sympathetic effect, which was usually only forty-five to ninety minutes, a period far shorter than the period of relief of pain.

DIAGNOSTIC VALUE OF INJECTION

While persistent localized tenderness over the scalenus anticus muscle with radiation of pain into the arm is a valuable diagnostic sign, it was present in only a small number of my cases. Slight or moderate tenderness was present in many cases, and no tenderness whatever could be elicited in a considerable number. Temporary paralysis of the scalenus anticus muscle produced by injection of procaine hydrochloride is a far more reliable method of estimating the role of the muscle in producing pain.

I made repeated attempts to demonstrate reduction of the radial pulse by rotating the head toward the affected side, extending the neck

and forcibly depressing the shoulder, but I was not able to identify a change in the pulse in any case. In 4 cases repeated measurements of the blood pressure on both sides, with the scalenus anticus muscle alternately tense and relaxed, showed no significant changes. Measurements of the blood pressure after injection also showed no changes. In 1 case oscillometric readings were made under similar conditions, and no significant changes were observed.

It is therefore likely that the glossy skin, muscle atrophy and coldness of the hand occasionally observed originate from irritation of the sympathetic nervous system rather than from actual compression of the subclavian artery.

SUMMARY AND CONCLUSIONS

Injection of procaine hydrochloride into the scalenus anticus muscle was used to determine the origin of pain in the shoulder in 40 patients. I gave 78 injections without serious untoward effects.

Injection of procaine hydrochloride into the scalenus anticus muscle is often accompanied by temporary anesthesia of the cervical sympathetic fibers.

Injection of procaine hydrochloride into the scalenus anticus muscle is a valuable diagnostic measure in determining the origin of pain in the distribution of the brachial plexus.

Injection of procaine hydrochloride is a therapeutic measure of some value when there is spasm of the scalenus anticus muscle of postural origin, due to trauma or to subdeltoid bursitis of the acute or chronic type.

Repeated injections may help to avoid the need for scaleniotomy.

PAPILLOMA OF THE CHOROID PLEXUS

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Papilloma of the choroid plexus is a rare tumor; no single author's published experience encompasses more than 12 instances. For this reason alone it seems justifiable to collect the isolated reports, since the frequency of diagnosis and surgical treatment of tumors of the brain is ever increasing and since there are few persons with a neurosurgical or neuropathologic experience extending over a period of five years who have not had contact with at least 1 papilloma. This paper represents a collection of the 80 odd published case reports of papilloma of the choroid plexus, together with some emphasis on incidence, sites of origin, inferences as to growth characteristics, pathologic picture—with emphasis on the known seeding characteristic—and summarized surgical experience.

INCIDENCE

Cushing's series of 2,023 tumors of the brain contained 12 papillomas of the choroid plexus; Elsberg's series of 878 contained 2; Tooth's series of 258 contained 3, and Peers's series of 188 contained none. In the aggregate of these series, then, the incidence is not quite 0.4 per cent, a figure that compares favorably with Cushing's published incidence of 0.5 per cent in his own series of tumors of the brain.

Table 1 shows the incidence of the tumor in relation to age. It is seen to occur at any age, with a great predilection for the first decades of life, a fact which is not generally appreciated, since the older reports are of sporadic individual cases in which the patients were chiefly adults. More recently, with the increased vigilance concerning tumor of the brain greater and greater numbers of papillomas occurring in children have been reported; indeed, in 1 case (Drucker), the patient was a full term stillborn baby. With patients grouped by decades, it now seems that the greatest incidence falls in the first decade of life.

Table 2 shows the incidence of the tumor at its favorite sites of primary growth. It will be noted that in this series the lateral ventricles and the fourth ventricle, with equal incidence, were the most favored sites, followed by the third ventricle. Of the tumors listed as of the third ventricle, 2 had extensions into the fourth ventricle by way of the aqueduct of Sylvius; 2 had extensions into one lateral ventricle, and 2 had extensions into both lateral ventricles by way of the foramens of Monro, so that only 6 were confined to the third ventricle. Van Wagenen

has pointed out that of the lateral ventricles the left is the one of predilection, and this observation is borne out by the present material (table 2). It seems justifiable to accentuate the fact that about 1 of 5 of the tumors occurring in the posterior fossa arises from the tufts of the choroid plexus that extend into or through the foramens of Luschka.

TABLE 1.—*Incidence of Tumor in Relation to Age*

Newborn to 11 months	9
1 year to 9 years	18
10 years to 19 years	11
20 years to 29 years	16
30 years to 39 years	9
40 years to 49 years	11
50 years to 59 years	6
60 years to 69 years	2
70 years to 79 years	1

TABLE 2.—*Incidence of Tumor in Relation to Site of Origin*

	Right Lateral Ventricle	Left Lateral Ventricle	Both Lateral Ventricles	Third Ventricle	Fourth Ventricle	Foramen of Luschka	Spinal Cord
	14	20	1	13	29	7	1
Total		35		13		36	1

TABLE 3.—*Location of Primary Tumor in Relation to Age*

	Lateral Ventricles	Third Ventricle	Fourth Ventricle	Spinal Cord
Newborn to 11 months	8	1	..	..
1 year to 9 years	14	1	3	..
10 years to 19 years	2	3	6	..
20 years to 29 years	4	2	10	..
30 years to 39 years	1	2	6	..
40 years to 49 years	5	1	5	..
50 years to 59 years	1	2	1	1
60 years to 69 years	1	1	..	..
70 years to 79 years	..	..	1	..

This location has been mentioned previously as an occasional site (Bailey; Cushing), but such a designation is definitely an understatement for this material.

Table 3 is perhaps the most informative of this series. It shows that within the first decade of life the tumor is almost exclusively one of the lateral ventricles, while in the second, third, fourth and fifth decades it may occur anywhere but most commonly occurs in the fourth ventricle. The discrepancy in the total numbers of cases in this and in the following tables is of course due to incomplete data in the several individual reports included in the tables.

The data available were not often complete enough to make possible any valid statement relative to the relation existing between this tumor and the sex of the host.

PATHOLOGIC CONSIDERATIONS

In the gross, papilloma of the choroid plexus is granular in appearance; it is grayish red to pinkish gray, according to the abundance of its blood supply, and often, particularly in the lateral ventricles, it bears a thin encasing membrane. This membrane may be closely applied to the papillae of the tumor or separated from it by an abundance of fluid so that the whole tumor has the appearance of a cyst with a mural nodule. In fixed specimens the membrane is more obvious, as is the cauliflower-like papillary arrangement of the tumor. Microscopically, the membrane is very delicate, at most only two to three cells in thickness. It is highly acellular, composed of the same type of tissue as the stroma of the papillae of the tumor and frequently rather heavily infiltrated with wandering cells of various kinds (fig. 1).

Histologically the stroma of the tumor is composed of delicate strands of very acellular, reticular, fibrous connective tissue (never glia),

TABLE 4.—*Site of Primary Tumor and Incidence of Seeding*

Lateral Ventricles	Third Ventricle	Fourth Ventricle	Spinal Cord
4	4	5	1

through which passes at least one capillary. The stroma is made up of primary and secondary stalks, and the subdivisions of the vascular tree of the individual papillae parallel the divisions of the connective tissue stalks. The epithelial covering is usually a single layer of cuboidal or low columnar cells which bear no cilia. In the more hyperplastic areas of the tumor the epithelial cells may be heaped up, without definite stratification but obviously with more than one layer. The cytoplasm of the epithelium is eosinophilic, and the nucleolus is usually in a basilar or middle position and deeply basophilic. The cytoplasm bears no blepharoplastin (Mallory) but has numerous vacuoles and basophilic and pigment granules that have elicited the attention of various investigators (Ciaccio and Scaglione; Davis; Zalka). In the cross section the epithelium is arranged circularly about the connective tissue core and its blood vessels.

Deposition of calcium in this type of tumor has been infrequently reported. It occurs in areas of degeneration and necrosis. No particular pathologic significance is attached to this, since calcified glomuses are frequently seen in normal brains and since Zalka has described this phenomenon as observed in the plexuses of old persons and of persons dying of non-neurologic and chronic diseases.

The seeding of this tumor was emphasized by Van Wagenen. Table 4 shows the incidence of seeding and the location of the primary tumor. When it is remembered that 2 of the tumors of the third ventricle had extensions into a lateral ventricle, it will be seen that the percentage

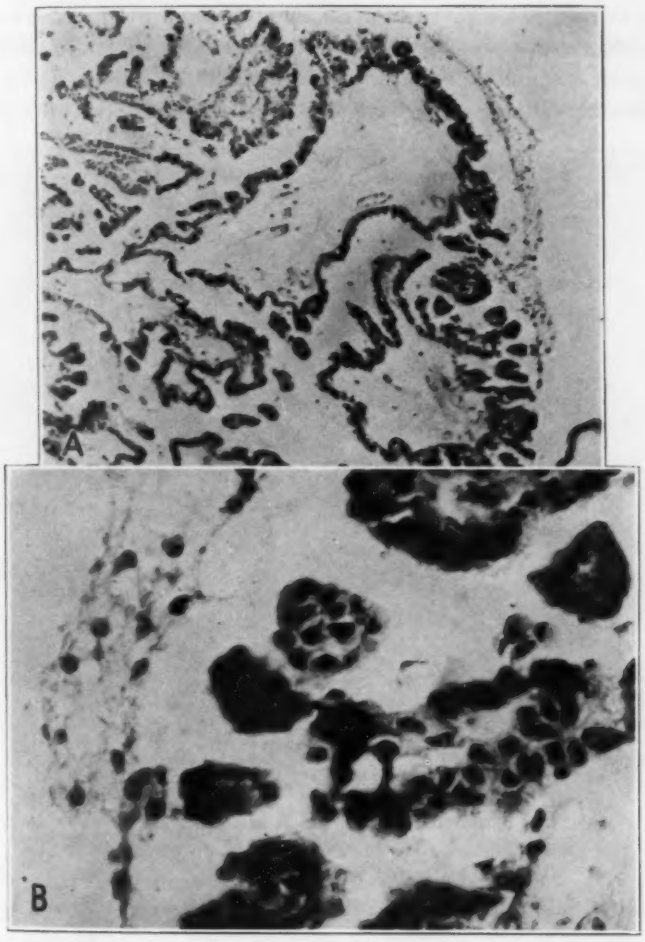

Fig. 1.—*A*, characteristic appearance of the tumor, showing its acellular stroma and delicate membrane. *B*, high power photomicrograph of *A*, showing the delicate membrane with infiltration of wandering cells.

of seeding is highest with tumors of the lateral ventricles. This is interpreted as evidence of viciousness in tumors of this location, as is the fact that in one third of the cases of seeding the phenomenon occurs within the first decade of life. From these observations, it is perhaps justifiable to conclude that had not the tumor killed its host early

the incidence of seeding from the lateral ventricle would be much higher. The explanation for seeding is obscure, but a ready assumption is that trauma to a wildly growing tumor mass within a dilated ventricle—and there is almost universally associated internal hydrocephalus—disengages tumor cells, which are carried away by the cerebrospinal fluid. Seeding appears to take place by way of the cerebrospinal fluid, since all secondary implants save possibly that in the single case of Hall and Fentress have shown the nodule to be in the subarachnoid space (fig. 2). The entire number of cases in which seeding occurred represents one fifth

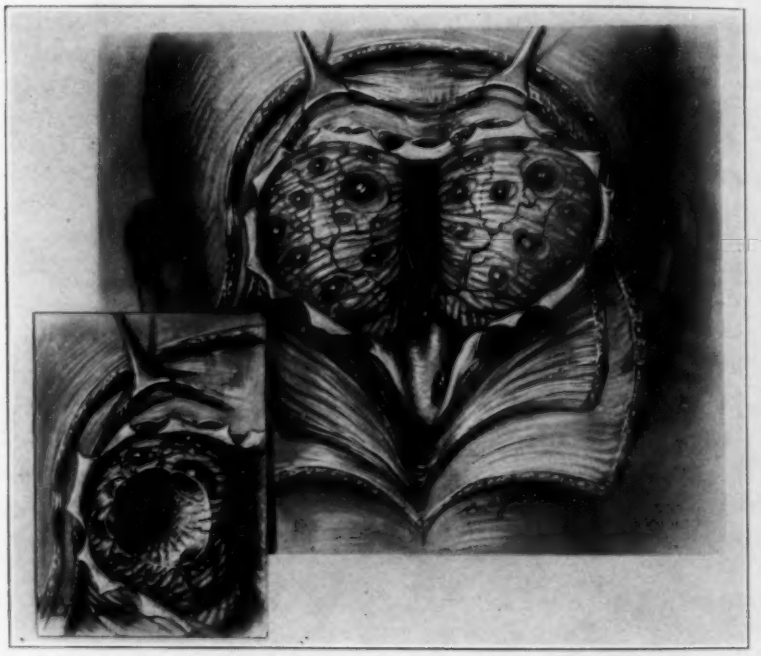

Fig. 2.—Drawing of the tumor in Van Wagenen's case 3, showing secondary implants under the arachnoid over the cerebellar hemispheres.

of the cases collected in this paper. It should be pointed out, however, that the recent greater number of surgical cases, as contrasted with the early autopsy cases, in a measure precludes the discovery of secondary nodules.

This tumor, particularly in the German literature, is frequently spoken of as a carcinoma. Academically and by strict definition this designation may be correct, since mitotic figures, reduplication of the epithelial layer, degeneration, necrosis and secondary distant growths are seen. But these signs of malignancy have not as yet been encountered in any single tumor reviewed in this series. Furthermore, all of the

intracellular changes save the appearance of mitotic figures have been observed in normal choroid plexuses in patients who died of a non-neurologic or chronic disease (Zalka; Ciaccio and Scaglione). In no instance has there been definite evidence of invasion of adjacent brain with obliteration of adjacent ependyma or pia; of neighboring glial reaction, such as occurs at the margins of an invasive primary or secondary neoplasm (Cox; Hassin), or of appearance of ciliated epithelium—the condition which normally obtains in embryonal and very young epithelium of the choroid plexus. Occasional mitotic figures are, more-

Fig. 3.—Photomicrograph of a secondary implant from the tumor shown in figure 2. Note that the tumor is not invading, but is pushing aside, the cerebellum.

over, often encountered in benign neoplasms. For these reasons it is doubted that papilloma of the choroid plexus is ever carcinomatous, with the ugly intimations that the term carries (fig. 3).

Internal hydrocephalus is an almost universal accompaniment of this kind of tumor. One notable exception to this rule was observed in the case reported by Hall and Fentress, in which the main body of the tumor was in the lumbar portion of the cord and smaller nodules occurred in the lateral ventricles. This condition, internal hydrocephalus, obtains whether or not there is mechanical obstruction to the circulation of

cerebrospinal fluid. This brings up the question whether by virtue of the increased secretory surface of the tumor there is an overproduction of cerebrospinal fluid. Illustrative cases in support of this contention are abundant in the literature, the most notable one being that reported by Davis, in which there was no obstruction but an enormous hydrocephalus in association with what was called hyperplasia of the choroid plexuses of both lateral ventricles. Further evidence can be gained from an occasional case in which an enveloping membrane is present. In such circumstances it is not infrequent to find the tumor existing as a mural nodule with its epithelium showing various degrees of degeneration, necrosis or ulceration and with its membrane greatly distended with a large volume of highly xanthochromic fluid. When the seedings and the adjacent structures are examined histologically, it is always seen that the tumor nodule proper is surrounded by a lake of fluid which presses aside the pia and the brain on one side and the arachnoid membrane on the other. Again, an overabundance of cerebrospinal fluid was noted in the cases of Guillain and his associates and of Fehr. For a period of days Fehr's patient, who was thought to have serous posttraumatic meningitis, had from 200 to 300 cc. of cerebrospinal fluid withdrawn daily by lumbar puncture. So it seems more than probable that the tumor mass functions in the capacity of a normal choroid plexus and that the associated internal hydrocephalus in those cases in which it is not due to a mechanical obstruction is most probably due to an overproduction of cerebrospinal fluid.

TABLE 5.—*Duration in Months of Symptoms in Various Age Groups*

	Months																			
	1 or Less	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36	42	48	54	60	84
Newborn to 11 mo..	4	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1 to 9 years.....	4	..	..	1	1	..	..	2	..	1	..	..	..	..	..	..	..	..	..	..	..
10 to 19 years.....	..	..	..	..	..	..	..	..	..	..	..	2	..	1	1	1	..	..	..	1	..
20 to 29 years.....	2	1	1	3	..	1	1	..	..	..	..	..	1	..	..	..	..	1	..	..	..
30 to 39 years.....	..	..	..	1	..	2	..	..	..	..	..	1	..	2	..	..	..	..	..	..	..
40 to 49 years.....	..	1	..	..	..	..	1	..	..	1	1	..	..	..	..	..	..	..	..	1	1
50 to 59 years.....	..	..	..	..	..	1	..	..	..	..	..	1	..	1	..	..	..	..	..	..	..
60 to 69 years.....	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
70 to 79 years.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1

LIFE HISTORY AND GROWTH CHARACTERISTICS OF THE TUMOR

Table 5 gives some notion of the life history of this tumor. If one were to plot the curve of relations expressed here, it would be a slightly curvilinear relation, with rapid progress of symptoms in the first decade of life and a gradual prolongation of the progress of symptoms as the higher decades were reached. This type of curve does not show a point to point relation between the site of the tumor and the progress of symp-

TABLE 6.—*Cerebrospinal Fluid in Cases of Papilloma of the Choroid Plexus*

Author	Pressure, Mm. H_2O	White Blood Cells per Cu. Mm.	Protein, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	Comment
Grandclement and others	500-700 560	1 ..	44 ..	.. ..	.. ..	Positive Pandy reaction
Van Wagenen no. 1	Increased	0	225	43.5	720	Clear (right ventricle)
	Increased	Many crenated R.B.C.	2,062	54	708	Xanthochromic (left ventricle)
	Normal	0	240	57	708	Clear (lumbar sac)
no. 2	Increased	27	..	..	..	Globulin, 3+
Gromelski	250	712	..	..	..	Xanthochromic
Vincent and others, no. 2	..	4	18	..	..	
Dandy, no. 2	Increased	..	..	..	..	Xanthochromic ventricular fluid on tumor side; clear on opposite side
Faber	200	3	760	..	..	Clear and colorless
Kellner	170	3	..	..	..	Clear; globulin reaction negative
Hall and Fentress	250	7	..	..	..	Slightly xanthochromic; globulin, 3+
	350	2	..	..	..	
Graves and Fleiss	Normal	Many R.B.C., normal W.B.C.	..	..	..	Smoky and xanthochromic; no pellicle; no bacteria
Obarrio and others	350	..	..	..	..	Positive Wassermann reaction; positive globulin
Montanaro and Hanón	..	2	180	..	..	Negative Pandy, Nonne-Appelt and Weichbrodt reactions
Fehr	350	0	220	99	698	Cisternal fluid
Von Weber	..	3	40	..	..	Clear
Friedman and Solomon	..	..	..	..	..	"The spinal fluid was negative"
Bleyer and Siebert	Increased	Normal	..	..	..	Clear and colorless; no pellicle; no bacteria
Ebbs	..	..	Normal	Normal	683	Always blood tinged; never over 850 red blood cells per cu. mm.
Turner and Simon, no. 2	120 225	.. ..	.. ..	.. ..	.. ..	"Chemical examination was negative"
Saccone and Rosenthal	..	..	..	..	..	"Ayala index of 5 revealed nothing"
Weinstein no. 1	Increased	60	..	..	..	Clear and colorless
no. 2	Increased	..	..	..	..	Clear and colorless
no. 3	310	..	..	..	..	Xanthochromic
Somerford	..	..	..	..	..	Lumbar puncture "three times without abnormal findings"
Caron and Samson	700	2	67	..	..	.....
Jefferson and Jackson	..	..	1,800	..	..	Ventricular fluid xanthochromic on affected side, normal on opposite side
Herren	400	3	56	..	..	Clear and colorless

W.B.C.= white blood cells; R.B.C. = red blood cells.

TABLE 7.—*Relation of Site of Primary Tumor to Surgical Morbidity*

Lateral Ventricles		Third Ventricle		Fourth Ventricle	
Recovered	Died	Recovered	Died	Recovered	Died
9	5	1	3	13	4

toms. The explanation must lie, then, in difference in local growth characteristics of this kind of tumor at various ages. In general, neurosurgeons have come to think of a tumor of the fourth ventricle as being quick to produce symptoms and of a tumor of a lateral ventricle as being slow, simply on the basis of adjacency of vulnerable structures and mechanical obstruction. The fact that the opposite is true of papilloma of the choroid plexus seems to point to the interpretation that when this tumor occurs in a child it is more malignant in its local growth characteristics than when it occurs in an adult.

CLINICAL DIAGNOSIS

The clinical diagnosis of this tumor is a problem indeed. Its rarity causes it not to suggest itself as a diagnostic possibility. Furthermore, a perusal of table 8 shows, in the number of wrong diagnoses by competent observers, that it must possess few of the diagnostic earmarks of the more common tumors of the brain. Experience tells that one is fortunate if one can lateralize the neoplasm without the aid of air studies. Examination of cerebrospinal fluid is of little aid in diagnosis. Table 6 shows the findings in 26 cases in which these data were given. However, it is felt that a tumor of this kind should suggest itself in the case of an infant with signs of obstructive or communicating hydrocephalus, particularly when there are lateralizing cerebral signs and xanthochromic fluid can be aspirated by puncture of the fontanel or other puncture. In passing, it is emphasized again that this type of tumor in the child is extremely vicious, in that its symptoms are obscure; it grows to enormous size; it is surgically difficult to handle because of its vascularity; and it causes death quickly. On the other hand, papilloma of the choroid plexus in the adult is more benign, though often having histologically apparent malignant characteristics.

SURGICAL EXPERIENCE

Surgical experience with this tumor began with Bielschowsky and Unger (cited by Van Wagenen) in 1902, and no one has published experience with more than 12 cases. Van Wagenen has reported a successful operation on an 8 month old infant after high voltage roentgen therapy. Dandy has had the unenviable experience of successfully removing a large nodule from a 3½ year old patient only to have it recur in six months at the site of excision. Data have been obtained on 30 operative cases, in which there were 10 deaths, a surgical morbidity of 33 per cent. No complete data can be obtained from this material for an estimation of surgical mortality, but it cannot be over 33 per cent. The greatest morbidity is in the middle decades of life, as is the greatest recovery percentage, since in only a few instances has the diagnosis been made and operation attempted with a patient under the age of 10 years.

Despite this, there does not seem to be a greater morbidity in adults from papilloma of the choroid plexus than from any other tumor similarly located (table 7).

Little can be concluded from these data regarding the use of roentgen therapy. Van Wagenen noted a decrease in the vascularity and size of the tumor in his patient, an infant, following roentgen therapy. However, because of the great vascularity of the tumor, which necessitated the use of the endotherm loop, he was not able to obtain a satisfactory biopsy specimen at his first stage operation, so that no case is on record in which a histologic study was made before and after irradiation. It is most probable, however, that irradiation is of benefit, since Jefferson and Jackson, using subtemporal decompression and roentgen therapy, were able to prolong for two years the life of a patient who had a right lateral intraventricular tumor. The usual postoperative course for a papilloma in a lateral ventricle is much shorter than this when the tumor has been incompletely removed and roentgen therapy has been withheld. Sai recently has reported alleviation of symptoms in the case of a patient who was given only high voltage roentgen therapy. In this case, however, the diagnosis of papilloma of the choroid plexus was only presumptive.

Recurrence has been reported in only 1 case, that of a 3½ year old boy. The tumor recurred in six months and attained a size greater than when first attacked. From so few data one can only mention in passing that papilloma of the choroid plexus does recur.

REPORT OF A CASE

Miss N. MacN., a 32 year old nurse with an extremely good social, educational and achievement background, presented herself with the complaints of "gingham or calico" colored scintillating scotomas, blurred vision and occasional transitory attacks of diplopia appearing when she was overtired.

The patient could not accurately date the onset of her illness but put it at something less than a year previously. At that time she had occasional transitory "gingham" scotomas, appearing first when she was overtired but increasing in frequency up to the time of examination, when the scotomas were almost continuously present. Also during this interval there had been transitory attacks of diplopia, never on more than three or four occasions and always when the patient was greatly fatigued. However, during this interval she had noted some difficulty in quickly focusing her eyes on new objects. Three months prior to examination she had begun to be troubled by blurred vision. She consulted a lay oculist, who told her that her glasses were too strong and prescribed new ones, which did not improve her vision.

The patient said that for many years she had had some unsteadiness when whirling, as in dancing. This unsteadiness, which consisted of staggering to the left, had not become exaggerated in the course of her present illness. For two years there had been a subjective sensation of increase in length of the right leg and an increase in size of the right hip. The glove and shoe sizes had not changed. There were no other complaints.

TABLE 8.—*Summary of Collected Cases of Papilloma of Choroid Plexus*

Author	Age of Patient	Site of Primary Tumor	Seeded	Source of Material	Surgical Results	Comment
Cited by Van Wegenen						
Guerard	3 years	Right lateral ventricle	No	Autopsy		
Robin and Blondel	11 years	Fourth ventricle	No	Autopsy		
Levrat-Perroton	25 years	Fourth ventricle	No	Autopsy		
Le Blanc	60 years	Left lateral ventricle	Right cerebral cortex	Autopsy		
Kelley	11 years	Fourth ventricle	No	Autopsy		
Chouppe	42 years	Fourth ventricle	No	Autopsy		
Demange	8 years	Left lateral ventricle	No	Autopsy		
von Plath	3 years	Both lateral ventricles	No	Autopsy		
Audry	45 years	Left lateral ventricle	No	Autopsy		
Douty	17 years	Fourth ventricle	No	Autopsy		
Beneke	26 years	Third ventricle	Fourth ventricle	Autopsy		
Stroeber	1½ years	Left lateral ventricle	Left temporal horn	Autopsy		
Hess	31 years	Fourth ventricle	Fourth ventricle	Autopsy		
Luttgen	?	Third ventricle	No	Autopsy		
Auvray	?	Fourth ventricle	No	Autopsy		
Bruchanow	2½ years	Left lateral ventricle	No	Autopsy		
Henneberg	50 years	Third and fourth ventricles	No	Autopsy	.....	No localizing symptoms
Ribberts	?	Fourth ventricle	No	Autopsy		
Bielchowsky and Unger	43 years	Right foramen of Luschka	Both cerebral cortices	Operation	Death	Localized as a cerebral tumor
Vigouroux	?	Fourth ventricle	No	Autopsy		
Rheindorf	21 years	Fourth ventricle	No	Autopsy		
Slaymaker and Elias	11 years	Fourth ventricle	No	Autopsy		
Boudet and Clunet	45 years	Right lateral ventricle	No	Autopsy		
von Wilier	15½ years	Fourth ventricle	No	Autopsy		
Natonek	?	Fourth ventricle	No	Autopsy		
von Bouwdijk	57 years	?	Cerebellum and cerebral cortices	Operation	Death	
Weygandt	10 months	Left lateral ventricle	No	Autopsy		
Goodhard	6 months	Right lateral ventricle	No	Autopsy		
Körner	9 years	Right lateral ventricle	No	Autopsy		
Perthes	47 years	Left lateral ventricle	No	Operation	Recovery	
Lorenzini	10 years	Third ventricle	No	Autopsy		
Sachs	55 years	Fourth ventricle	No	Operation	Recovery	Correctly localized
Priesel	74 years	Fourth ventricle	No	Autopsy		
Okabe	5 months	Both lateral ventricles and third ventricle	No	Autopsy		

Okabe	5 months	Both lateral ventricles and third ventricle	No	Autopsy		
Noodt						
Case 1	33 years	Both lateral ventricles and third ventricle	No	Autopsy		
Case 2	1 year	Left lateral ventricle	No	Autopsy		
Davis and Cushing						
Case 1	22 years	Left foramen of Luschka	No	Operation	Death	Mislocalized preoperatively
Case 2	9 years	Left lateral ventricle	No	Operation	Death	Localized to left cerebellar hemisphere
Case 3	50 years	Left lateral ventricle	No	Operation	Recovery	Correct localization
Case 4	30 years	Right foramen of Luschka	No	Operation	Recovery	Localized to right cerebrum
Case 5	27 years	Fourth ventricle	No	Operation	Recovery	Correct localization
Case 6	28 years	Fourth ventricle	No	Operation	Recovery	Diagnosed as acoustic neurinoma
Töppich	2 years	Fourth ventricle	Basilar cisterns, cerebellum and cord	Autopsy		
Zalka	?	Fourth ventricle	No	Autopsy	.....	Incidentally found at necropsy
Grandclement and others	24 years	Left foramen of Luschka	No	Operation	Death	Localized to frontal lobe
Van Wagenen						
Case 1	3 months	Left lateral ventricle	No	Operation	Recovery	Diagnosed by xanthochrome intraventricular fluid
Case 2	13 years	Left lateral ventricle	Left temporal horn and right lateral horn	Autopsy	.....	Main tumor not correctly localized
Case 3 *	38 years	Lateral ventricles	Cerebellum	Operation	Recovery	Diagnosed as postfossal tumor
Case 4 *	30 years	Third ventricle	No	Operation	Recovery	Localized by ventriculography
Case 5 *	3 years	Fourth ventricle	No	Operation	Recovery	Correct localization
Case 6 *	1 year	Lateral ventricles	No	Operation	Death	Localized by ventriculography
Case 7 *	28 months	Left lateral ventricle	No	Operation	Death	Death on second operative attack
Case 8 *	4 years	Fourth ventricle	No	Operation	Recovery	Localized correctly; patient died 4 years later of influenzal meningitis
Gromelski	50 years	Spinal cord	Right calcarine cortex	Autopsy		
Vincent and others						
Case 1	36 years	Fourth ventricle	No	Operation	Recovery	Diagnosed as cerebral tumor; localized by ventriculography
Case 2	26 years	Fourth ventricle	No	Operation	Recovery	Localization by ventriculography
Guillain and others	47 years	Right foramen of Luschka	No	Operation	Recovery	Diagnosed as acoustic neurinoma
Cushing	22 years	Fourth ventricle	No	Operation	Recovery	
Dandy						
Case 1	17 years	Third ventricle	No	Operation	Death	Localized by ventricular estimation
Case 2	14 years	Right lateral ventricle	No	Operation	Recovery	
Case 3	3½ years	Right lateral ventricle	Recurrence	Operation	Recovery with recurrence	Clinically localized to postfossa

* These unpublished cases are from the department of surgery, division of neurologic surgery, Rochester School of Medicine and Dentistry. Dr. William P. Van Wagenen gave permission to use this material.

TABLE 8.—*Summary of Collected Cases of Papilloma of Choroid Plexus—Continued*

Author	Age of Patient	Site of Primary Tumor	Seeded	Source of Material	Surgical Results	Comment
Faber	29 years	Right lateral ventricle	No	Autopsy	.....	Diagnosed as unlocalized cerebral tumor
Kellner	34 years	Fourth ventricle	Cerebellum	Autopsy	.....	Diagnosed as cerebral tumor
Hall and Fentress	61 years	Third ventricle and left lateral ventricle	Cerebrum, cerebellum, spinal cord	Autopsy	.....	Diagnosed as metastatic tumor of cord
Graves and Gleiss	9 months	Left lateral ventricle	No	Autopsy	.....	Unlocalized during life
Fincher	26 years	Right lateral ventricle	No	Operation	Recovery	Localized by ventriculography
Obarrio and others	30 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Montanaro and Hanon	29 years	Left foramen of Luschka	No	Autopsy	.....	Localized correctly
Fehr	23 years	Fourth ventricle	No	Autopsy	.....	Diagnosed as serous meningitis
Von Weber	42 years	Left lateral ventricle	No	Operation	Death	Diagnosed as temporal lobe glioma
Tönnis						
Case 1	14 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Case 2	18 years	Right lateral ventricle	No	Operation	Recovery	Diagnosed as temporal lobe glioma
Friedman and Solomon	20 months	Left lateral ventricle	No	Autopsy	.....	Localized to left hemisphere
Bleyer and Siebert	6 months	Left lateral ventricle	Left lateral ventricle	Autopsy	.....	Diagnosed as tuberculous meningitis
Ebbs	14 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as idiopathic hydrocephalus
Turner and Simon						
Case 1	27 years	Third ventricle	No	Operation	Death	Unlocalized
Case 2	55 years	Third and fourth ventricles	No	Operation	Death	
Saccone and Rosenthal	48 years	Fourth ventricle	No	Autopsy	.....	Diagnosed as multiple sclerosis
Weinstein						
Case 1	10 weeks	Left lateral ventricle	No	Autopsy	.....	Diagnosed as meningitis because of pleocytosis
Case 2	14 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as tumor of right cerebral hemisphere
Case 3	45 years	Left lateral ventricle	No	Operation	Death	Localized by ventriculography
Cohen	43 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Somerford	7 years	Third ventricle and left lateral ventricle	No	Autopsy	.....	"No localization possible"
Tudos	11 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as hydrocephalus
Caron and Samson	41 years	Third ventricle	No	Autopsy	.....	Correct localization
Jefferson and Jackson	26 years	Right lateral ventricle	No	Operation	Recovery	Localized by ventriculography
Drucker	Newborn	Left lateral ventricle	No	Autopsy	.....	Tumor measured 4 × 3 × 3 cm. at birth
Herren	32 years	Left foramen of Luschka	Vermis	Operation	Death	Localized by ventriculography

The patient's family stated that within recent months she had shown personality changes in the direction of forgetfulness, sloppiness in her work, apathy and general decrease in sociability.

The past history and family history were noncontributory.

The general physical examination showed her to be tall (5 feet 7 inches; 170 cm.), slender (112 pounds; 50.8 Kg.) and asthenic, without positive abnormalities. Measurements of the long bones of the two sides were identical, as were measurements of the two sides of the pelvis.

The neurologic examination revealed the following positive signs: The vision was normal; the fields were full, with a slight enlargement of the blindspots. There were no objective scotomas. There was bilateral choking of the disks (4 D.). There was nystagmus, both horizontal and rotary, on extreme left lateral gaze. There was no diplopia. Otherwise the cranial nerves were normal.

The motor and sensory systems were without positive abnormalities. There was a slight degree of dysdiadokokinesis of the left hand as the only symptom referable to the cerebellar system.

The deep tendon and superficial reflexes were present, normal and equal, and there were no pathologic reflexes and no clonus.

There were no signs, either primary or neighborhood, involving any of the cerebral centers.

The patient was seen by two neurologic consultants, both with wide experience, who reported essentially the same findings. The diagnoses of the three consultants were: hydrocephalus, cause unknown, and tumor of the brain, unclassified, of the left side of the cerebellum and of the right frontal area.

The patient was admitted to the hospital. Roentgenograms of the sinuses were normal; roentgenograms of the skull showed only a slight forward shift of the calcified pineal gland. The Kolmer reaction of the blood was negative. Routine studies showed the blood and the urine to be well within normal limits. A lumbar puncture was done with the patient in the reclining position and showed clear, colorless fluid under an initial pressure of 400 mm. of water; 3 lymphocytes per cubic millimeter of fluid, and a level of total protein of 56 mg. per hundred cubic centimeters. A Kolmer test of the spinal fluid gave a negative reaction.

Subsequent neurologic examinations showed only an equivocal Babinski sign on the right and bilateral unsustained patellar clonus.

On Dec. 19, 1939, a ventriculogram was made, air being injected only into the left lateral ventricle. Subsequent roentgenograms showed a moderate degree of symmetric dilatation of the lateral and third ventricles. No air could be visualized in the fourth ventricle, despite two attempts by routine manipulation. A cerebellar craniotomy was immediately performed. Before the very tight dura of the posterior fossa was opened, a right ventricular tap was attempted. A subcortical vessel was ruptured and bled briskly. The needle was left in place until the bleeding stopped. Then the left lateral ventricle was tapped, and clear fluid was recovered. The dura of the posterior fossa was then opened widely, and after the arachnoid of the cisterna magna was opened a grayish brown granular tumor was seen under the left lobus biventer, presenting over the left tonsil and extending through the foramen magnum onto the spinal canal to the second cervical vertebra. The lower pole of the tumor was dissected free, but the tumor was fragmented in its removal. The origin of the upper pole was not positively identified, but the operator felt that he was dealing with a psammomatous meningioma arising from the basilar portion of the occipital bone and that by luck rather than by skill he had dissected off the attachments to the basilar artery. The three large fragments that were preserved measured 2 by 2 by 1 cm. each

and weighed 6.5 Gm. These fragments the operator felt represented three fourths of the tumor. The dura over the cerebellum and the upper part of the cord was left open and the wound closed in layers in the usual fashion.

The immediate postoperative course was characterized by great restlessness without threatening changes in the vital signs. The patient was disoriented and irrational and showed hypesthesia on the left side and increase in the reflexes, with ankle and patellar clonus and a Babinski sign on the left. Daily lumbar punctures showed an increase in pressure, with the fluid at first rather bloody but clearing of free blood in two days. Choking of the disks did not subside. It was felt that probably bleeding from the subcortical vessel ruptured at the time of ventricular tap had allowed the collection of a subdural hematoma on the right side. Two days later, exploratory burr holes in the right temporal and frontal region failed to reveal subdural blood of clinical significance. The surgical specimen was at this time available for microscopic examination, and the tissue was readily seen to be a papilloma of the choroid plexus. Because the patient's condition had not improved, it was felt that most probably there was a tumor mass filling the fourth ventricle and that at the first operation only its extension through the foramen of Luschka had been removed. Six days after the original operation the cerebellar wound was reopened and a large accumulation of xanthochromic fluid was encountered. The right lateral ventricle could not be entered, but the left was readily tapped. The fourth ventricle was explored through the left lateral recess and by splitting the vermis; no tumor tissue was encountered. The patient's condition after this was unchanged. Several days later an attempt was made to tap the right ventricle again, and 40 cc. of chocolate-colored blood was aspirated. This was followed by clear cerebrospinal fluid. It was felt that an intraventricular clot had formed at the time of the first operation and that this procedure had drained it and ruptured its wall into the cerebrospinal fluid circulation. The patient complained bitterly of headache, vomited a great deal and was almost continuously nauseated for the next four days. Lumbar punctures, which up to this time had yielded clear fluid, now yielded deeply xanthochromic fluid, which cleared subsequently. The patient, after her early headache and vomiting, was clear mentally, sat up in bed and ate well.

The signs referable to the upper motor neurons disappeared, but low grade choking persisted. Subsequently and slowly she became drowsy and irresponsive. A ventricular tap yielded clear fluid with flecks of fibrin. Some methylene blue was introduced into the right lateral ventricle and was not recovered from either the left ventricle or the lumbar sac. With the patient in the cerebellar position, needles were introduced into the posterior bodies of both lateral ventricles and a third into the anterior body of the right through the previously placed burr holes. The right ventricle was emptied and gently irrigated. Some perfusion fluid with phenolsulfonphthalein was introduced under low pressure into the left ventricle and recovered from the anterior needle in the right ventricle. The process was repeated, perfusion through the anterior needle in the right ventricle until all air had been emptied from the two ventricles and the perfusion fluid recovered from both posterior needles. Subsequent lumbar puncture failed to recover the dye. After this the patient's course was slowly downhill, and she died on March 8, 1940, after a long interval of unconsciousness.

Postmortem examination of the brain revealed dense, impermeable adhesions that bound the cerebellum to the floor of the left lateral recess and also the vermis to the obex. There was, then, an obstructive internal hydrocephalus. Further sections revealed on the right side a large intracerebral hemorrhagic cavity the wall of which was lined by shaggy, necrotic brain and encapsulated firm blood clot.

A point of communication between this hemorrhagic cavity and the right lateral ventricle was identified, and the wall of that ventricle was stained with blood pigment and covered with a thin layer of organized fibrin. On the inferior surface of the vermis was a second plaque of tumor.

SUMMARY

Eighty odd cases of papilloma of the choroid plexus are reviewed and the pathologic considerations mentioned. It is pointed out that the recent literature emphasizes the occurrence of this tumor in childhood as a tumor almost exclusively of the lateral ventricles, while in adulthood it is most likely to occur in the fourth ventricle. The growth characteristics of the tumor in each age group are mentioned; the occurrence of seeding is reemphasized; the difficulty in clinical diagnosis is noted, and the surgical experience with this tumor is reviewed. A case report is included.

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PRIMARY TORSION AND INFARCTION OF THE APPENDICES EPIPLOICAE

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Among the many acute intra-abdominal conditions which produce clinical problems, primary lesions of the appendices epiploicae are relatively rare. Because of this, the clinician or surgeon often does not consider lesions of these structures in the differential diagnosis of intra-abdominal disease. Consequently the clinical diagnosis of primary torsion, infarction or inflammation of the appendices epiploicae has, according to the literature on this subject, never been made. One must admit, however, that recognition of disease of these structures is very important from the standpoint of offering the patient an accurate prognosis. There are many variations from the typical picture, and often the clinical and laboratory findings are not sufficiently significant to be of any help in diagnosis. Our object in conducting this review was to discover, if possible, any facts that could add to our diagnostic acumen when confronted with the aforementioned conditions.

In 1936, Fiske [1] was able to collect only 42 cases of primary disease of the appendices epiploicae from the entire medical literature; he added 2 of his own cases. Since then, other instances of this condition have been reported by Davis,[2] Walker,[3] Piulachs,[4] Poirier,[5] Micheli,[6] Baumeister, Hargens and Morsman [7] Campbell [8] and Eliason and Johnson.[9] In all, these cases comprise a total of 55 reported to date.

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In the period between 1915 and 1939, 7 cases of primary acute lesions of the appendices epiploicae were observed at the Jewish Hospital. In no case was a correct diagnosis of the condition made preoperatively; the lesion was discovered at operation only after thorough exploration of the peritoneal cavity failed to reveal any other cause for the acute abdominal episode. There is no train of symptoms or signs characteristic of this disease. Occasionally abdominal pain is the only presenting symptom; this may be definitely localized or vague and ill defined. Usually symptoms referable to the vermiform appendix are so predominant that attention is likely to be diverted from the underlying abnormality. The clinical importance of recognizing the true etiologic factor is obvious. It is our purpose, therefore, to describe this syndrome and to discuss the pathologic mechanism of its production.

ANATOMIC CONSIDERATIONS

The epiploic appendages are small pouches of peritoneum laden with fat. Each appendage encloses small branches of the arteries and veins which vascularize the corresponding segment of the colon. The appendages are situated along the cecum, the colon, the upper part of the rectum and occasionally also the vermiform appendix. They are chiefly found along the transverse and pelvic segments of the colon, where they are larger than elsewhere; at the base of the appendix they are usually rudimentary. The appendices epiploicae also bear a definite relation to the taeniae coli and are often arranged in two rows, one situated medial to the anterior taenia and the other lateral to the posterolateral taenia. They rarely appear in three rows and less often in one row. The altered position of the suspended transverse colon changes the relative position of the taeniae and consequently also of the appendices epiploicae; the anterior taeniae become posteroinferior, and the posterolateral taeniae become anterior.

The epiploic appendages vary considerably in size, shape and contour in various parts of the colon; as a rule they are longest in the sigmoid flexure. However, the size appears to vary also with the general state of body nutrition; they are largest and most conspicuous in obese persons and in those who have recently lost weight. The latter fact indicates that the fat in the appendages is utilized more slowly than is the remaining body fat. The average length of the epiploic appendage is 3 cm.; these structures have been reported, however, to have reached a length of 15 cm. (Linkenfeld [10]). They vary in shape, being tubular, saccular, cylindric, multilobulated, conical or leaf shaped. The free borders may be flat, rounded, serrated, fringed or indented. Their attachment to the intestinal wall may be by a wide or a narrow base. In children the

10. Linkenfeld, F.: Deutsche Ztschr. f. Chir. **92**:383, 1908.

appendices epiploicae are more or less inconspicuous, but they have been shown to appear as early as the fifth month of fetal life.

The physiology of the appendices epiploicae is still not clearly defined and is the subject of much controversy. A review of the literature reveals several conceptions which appear to be based more on supposition than on actual fact. Thus Robinson [11] in his monograph concluded that the appendices epiploicae are associated with the movement and absorption of fluids in the large bowel. Other investigators have expressed the belief that they serve as protective agents, like the omentum, and act as barriers against injury. In support of the latter idea is the fact that they are often found adherent to areas which are the seats of inflammatory reactions. However, this agglutinative property is characteristic of all peritoneal surfaces. Patterson [12] suggested that they may act as protective external colonic pads, thus enabling the colon to ward off the adjacent organs in its peristaltic excursions. Cheever, in a discussion of Patterson's paper, stated the opinion that the appendices epiploicae are entirely functionless.

In spite of the voluminous literature on this subject, we were impressed with the need for a painstaking study of the anatomic and physiologic aspects of the appendices epiploicae. For this reason a detailed study of these structures was conducted by one of us (B. P.). The blood vessels to the colon were injected with a mixture of red lead and starch in order to trace the smaller branches to their terminations in channels of the intestinal wall.

It was noted that the vessels to the large bowel do not enter the wall directly at the mesenteric border as do the vasa recti of the small intestine. Instead, they divide at the mesenteric border of the colon within the peritoneal fat; then they encircle the wall of the bowel subperitoneally, giving off small branches to the wall. In so doing they carry along a layer of protective subserous fat which is directly continuous with the fat in the mesentery. The main vessels continue into the fat of the appendices epiploicae, where they generally describe an inverted U-shaped arch from which branches run into the intestinal wall proximally and into the epiploic fat distally. The main vessel finally enters the intestinal wall adjacent to the border of the tenia (fig. 1). It appears, therefore, that the appendices epiploicae are merely protective fat pockets for the redundant intestinal vessels when the intestinal wall is collapsed. This safety mechanism of vascular redundancy is obviously necessary to prevent compression of the vessels and obliteration of their lumens when the bowel is distended. In all probability also the appendices epiploicae

11. Robinson, R.: Anatomie et pathologie des séroappendices, Thesis, Paris, no. 282, 1908.

12. Patterson, D. C.: New England J. Med. **209**:1255, 1933.

have some protective and absorptive function, since they consist of vascular tissue covered by peritoneum similar to the greater omentum. In contrast to the omentum, however, their surface area is small, and their vascularity is not as great; this reduces their functional capacity to a minimum.

There follow reports of 7 cases of acute lesions of the appendices epiploicae which have been observed at the Jewish Hospital. The lesions are of interest from the standpoint of difficulty of recognition, and the data indicate that such lesions occur often enough to warrant consideration in all cases of acute intra-abdominal lesions, especially in adult obese patients.

Fig. 1.—Blood supply to the appendices epiploicae, showing the main blood vessel leaving the colon and entering the epiploic appendage, where it describes a U-shaped arch. After giving off branches to the appendix, the vessel reenters the colon.

REPORT OF CASES

Case 1.—E. D., a 42 year old white woman, was admitted to the hospital because of pain in the left lower quadrant of the abdomen of five days' duration. The pain was at times sharp and sticking and at others dull and achy; it had been especially severe during the past twenty-four hours. Two hours before hospitalization the patient felt "something give" within the abdomen, and the pain appeared to subside somewhat. She also complained of frequency of urination and had to urinate every half hour.

On physical examination the patient was seen to be obese. She was apparently not acutely ill. The temperature was 101 F., the pulse rate 100, the respiratory rate 20 and the blood pressure 130 systolic and 90 diastolic. There were exquisite tenderness and moderate spasticity in the left lower quadrant. Vaginal examination showed tenderness in the left fornix. The urine was normal. The blood count revealed 10,000 white blood cells per cubic millimeter, with 73 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 3 per cent monocytes.

The clinical impression was that of perforated sigmoiditis, for which she was operated on through a left gridiron incision. As the peritoneal cavity was opened, an irregular, firm mass was seen about the sigmoid flexure. The free surface of this mass was mottled yellow, gray, blue and red in different areas. It proved to be a twisted gangrenous epiploic appendage. The mass was excised after ligation of its base, and the patient made an uneventful recovery.

Pathologic examination of the specimen disclosed diffuse hemorrhagic extravasations and suppuration within a mass of fatty tissue.

CASE 2.—A. D., a 20 year old woman, was admitted to the hospital with the complaint of pain in the right lower quadrant of the abdomen, of two days' duration. The pain had been intermittently sharp and cramplike and had become progressively more severe. During the past twenty-four hours she had been suffering also from frequency of urination and dysuria.

The past history was essentially irrelevant except for occasional head colds and transient mild attacks of pain in the right lower quadrant of the abdomen since the age of 10 years. The menstrual history was normal; the last period had occurred three weeks before.

On examination the patient appeared well developed and well nourished but acutely ill. The temperature was 99 F., the pulse rate 80, the respiratory rate 20 and the blood pressure 132 systolic and 88 diastolic. There was marked tenderness in both lower quadrants of the abdomen, especially on the right side, where rebound tenderness was also elicited. Rectal examination revealed no abnormality; the urine was normal, and a normal blood count was recorded.

The clinical impression was that of acute appendicitis. At operation, through a right gridiron incision and with spinal anesthesia, the peritoneum was opened, and a large quantity of serosanguineous fluid was found in the peritoneal cavity. Attached to the ascending colon was a blue-black mass which measured 4 by 3 by 0.5 cm.; this proved to be a gangrenous epiploic appendage, the gangrene being caused by torsion. The mass could be easily separated from the bowel, and it was excised after ligation of its base. The vermiform appendix was also removed, and the patient made an uneventful recovery.

Pathologic examination of the epiploic appendage showed a hemorrhagic infarct caused by thrombotic occlusion of its venous system. The vermiform appendix appeared normal.

CASE 3.—L. H., a 28 year old woman, was hospitalized because of severe abdominal pains of eight days' duration. At its onset the pain was referred to the left lower quadrant, but on the fifth day of illness it radiated to the right lower quadrant. On the fourth day of the illness the pain was accompanied with chills and fever.

The menstrual period was normal; the last period had ended one week before the patient entered the hospital. She had been married for six years and had three children, who were living and well.

She was well developed and well nourished. She was very tender in the left lower abdominal quadrant and presented a small palpable mass in the left anterior lumbar region. The urine was normal. The blood count showed 16,100 white

blood cells per cubic millimeter, with 65 per cent polymorphonuclear leukocytes and 35 per cent lymphocytes. Roentgen examination of the kidneys revealed no abnormality. The clinical impression was that of sigmoiditis or diverticulitis of the colon.

With the patient under general anesthesia a midline incision was made in the lower part of the abdomen and the peritoneal cavity was entered. An irregular blue-black mass was found attached by means of a broad pedicle to the sigmoid flexure; all other abdominal viscera appeared normal. The mass as well as the vermiform appendix was removed, and the patient made an uneventful recovery.

Pathologic examination of the specimen revealed thrombotic occlusion of the epiploic veins with hemorrhagic infarction of the epiploic appendage. The vermiform appendix appeared normal.

CASE 4.—A. E., a 45 year old woman, was admitted to the hospital with pain in the lower part of the abdomen, of two day's duration. She had felt a mass in the middle of the lower part of the abdomen for one year, and she had suffered from dysuria for the past two months.

Her present illness dated from two years previously, when an umbilical herniaplasty was performed. After the operation the patient suffered from transient attacks of dysuria. One year before the onset of her present illness she felt a small, painless, hard mass in the middle of the lower part of the abdomen. Two days before entering the hospital she suddenly experienced severe pain and tenderness in the region of the mass. This had become progressively more severe, and there had been a moderate rise in temperature.

During the past two years the patient had become obese, and she had also noted a change in her menstrual cycle; menstruation had become irregular, and the flow was scant.

Examination revealed her to be obese and acutely ill. The temperature was 101 F., the pulse rate 90 and the respiratory rate 24. There was pronounced emphysema of the chest, and the heart was enlarged to the right and to the left of the sternum. The abdomen was pendulous and showed a transverse scar about 4 inches (10 cm.) in length in the region of the umbilicus. Below the scar there was a firm, round, nodular mass measuring about 2 inches (5 cm.) in diameter. It appeared to be connected with the abdominal wall and was very tender. The urine gave a 3 plus reaction for albumin; many epithelial and white blood cells and occasional granular casts were seen. The blood count showed 12,000 white blood cells per cubic millimeter, of which 80 per cent were polymorphonuclear leukocytes and 20 per cent were lymphocytes.

The preoperative impression was that of abscess of the abdominal wall. With the patient under general anesthesia a median incision was made below the umbilicus. An edematous, red-blue mass was found adherent to the anterior parietal peritoneum. Further investigation disclosed this mass to consist of five appendices epiploicae of the sigmoid, matted together and twisted about their pedicles. No other pathologic lesion was noted in the abdomen. The gangrenous appendages were excised, and the patient made an uneventful recovery.

Pathologic examination of the specimen disclosed hemorrhagic extravasations and round cell infiltration into the various fat lobules.

CASE 5.—S. H., a 20 year old man, was seized with a sudden attack of sharp pain in the epigastrium three days before entering the hospital. Twenty hours after the onset of his illness the pain became localized in the right lower quadrant of the abdomen, where it remained. It was associated with persistent nausea. The past history revealed a similar transient attack of pain seven months before.

Examination revealed the patient to be well developed and well nourished. He was apparently acutely ill. The temperature was 100 F., the pulse rate 120 and the respiratory rate 24. There were marked tenderness and slight muscle spasm in the right lower quadrant of the abdomen. The urine was normal. The blood count showed 10,200 white blood cells per cubic millimeter, of which 73 per cent were polymorphonuclear leukocytes and 27 per cent were lymphocytes.

A diagnosis of acute appendicitis was made. A right McBurney muscle-splitting incision was made with the patient under general anesthesia. Exploration of the peritoneal cavity disclosed a small yellow and red mass arising from the lateral cecal wall and adherent at one point to the mesoappendix. This mass was taken to be a gangrenous epiploic appendage, and it was excised. The vermiform appendix was also removed, and the patient made an uneventful recovery.

Pathologic examination of the specimens revealed an atrophic vermiform appendix and an infarcted epiploic appendage infiltrated with red and white blood cells.

CASE 6.—B. B., a 48 year old man, was admitted to the hospital with the complaint of pain in the right lower quadrant of the abdomen, of three days' duration. The pain was sudden in onset; it was sharp and intermittent, and it persisted until the patient entered the hospital. There were also a mild degree of nausea and a slight rise in temperature. The past history revealed that the patient had had a large reducible right inguinal hernia for the last twenty-five years, for the relief of which he wore a truss. This occasioned no unusual symptoms.

Examination showed him to be well developed and well nourished. He was apparently not acutely ill. The temperature was 99 F., the pulse rate 84 and the respiratory rate 24. The only salient findings were tenderness and slight muscle spasm in the right lower quadrant of the abdomen. There was also found an easily reducible right inguinal hernia. Rectal examination revealed no abnormality.

A diagnosis of subacute appendicitis was made. With the patient under general anesthesia, a McBurney muscle-splitting incision was made and the peritoneum was entered. The vermiform appendix appeared normal. Further exploration revealed a twisted red-blue gangrenous epiploic appendage of the transverse colon, which was loosely adherent to the anterior parietal peritoneum just below the level of the umbilicus. Appendectomy and excision of the epiploic appendage were performed, and the patient made an uneventful recovery.

Pathologic examination revealed a normal vermiform appendix and infarction of the epiploic appendage caused by venous thrombosis of its vessels.

CASE 7.—W. K., a 44 year old man, was admitted to the hospital with the complaint of abdominal pain, nausea, vomiting and fever of six days' duration. The onset of the attack was sudden, and the pain was cramplike, intermittent and localized to the epigastrium. Three days later the pain became increasingly more severe and shifted to the right lower quadrant of the abdomen. The temperature was slightly elevated but rose to 103 F. on the day of his entering the hospital. The patient had had two loose stools during the past twenty-four hours.

During the past three years he had been known to have pulmonary tuberculosis, and nine months previously he had been discharged from a sanatorium with arrested bilateral apical tuberculosis.

Physical examination revealed him to be well developed and well nourished. He was acutely ill. The temperature was 102 F., the pulse rate 112, the respiratory rate 28 and the blood pressure 114 systolic and 80 diastolic. There were dulness to percussion in the apex of the left lung and diminished breath sounds and moist rales in that of the right. There was tenderness over the entire lower part of the abdomen, especially on the right. There were also marked spasticity and

rebound tenderness in the right lower quadrant of the abdomen. Rectal examination showed tenderness on the right side. The urine was normal. The blood count showed 13,000 white blood cells per cubic millimeter, with 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes.

A diagnosis of acute appendicitis was made, although the possibility of ileocecal tuberculosis was also considered. With spinal anesthesia, a McBurney muscle-splitting incision was made. The peritoneum was thick and edematous, and free serosanguineous fluid was found in the peritoneal cavity. A thick, red, indurated mass about 8 cm. long, with a bulbous tip, was brought out from the region of the appendix. The mass was excised with the phenol knife after ligation of its base; the patient made an uneventful recovery. Subsequent examination of the sputum, the fluid from the peritoneal cavity, the stools and the urine revealed no evidence of tubercle bacilli. The Wassermann reaction of the blood was negative.

A study of the excised tissue showed on section closely packed yellow and red lobules of adipose tissue. Microscopic examination of the specimen disclosed lobules of fat separated by loose fibrous connective tissue septums and enclosing numerous dilated and engorged thin-walled blood vessels. There were also diffuse hemorrhagic extravasations within the fat lobules.

COMMENT

In summarizing the findings in our entire group we have tabulated the incidence of the disease according to age, sex, pain, etc. An analysis of the diagnostic facts regarding this disease shows that of the 7 patients whose cases are reported in this paper 4 were women and 3 were men. Their ages ranged from 20 to 48, with an average of 35.5. The salient features of these 7 cases are summarized in the accompanying table. The onset of symptoms was acute in all 7 cases. The average duration of symptoms before operation varied from two to eight days. The character of the pain varied; it was described as sharp by 4 patients, cramplike by 2 and dull by 1. In 2 patients the pain was localized immediately in the left lower quadrant; in 2 others, in the right lower quadrant, and in 1 it persisted in the middle of the lower part of the abdomen. In the remaining 2 patients the pain began in the epigastrium and later shifted to the right lower quadrant. Low grade fever occurred in 4 cases, nausea in 3, vomiting in 1, constipation in 1, loose stools in 1, dysuria in 2, and frequency of urination in 2.

Three patients presented past histories which may have had bearing on their present illness. Thus, in 1 instance the patient experienced transient attacks of pain in the right lower abdominal quadrant for ten years prior to the present attack of pain in the same quadrant; in 1 other there were transient attacks of abdominal pain similar to that noted before operation for seven months before the onset of the present illness. In the last case the patient had been operated on for an umbilical hernia two years previously. She noted a mass below the umbilical scar one year after the hernioplasty; this mass proved to be a large infarcted epiploic appendage.

Physical examination revealed that 5 patients were well nourished and 2 were obese. Only 3 patients appeared acutely ill on entering the hospital. The average temperature varied from 99 to 102 F.; in 4 instances it was 100 F. or over. Tenderness over the affected area was observed in all cases. In 2 patients it was located in the right lower quadrant; in 2, in the left lower quadrant; in 2 over the entire lower part of the abdomen, especially on the right side, and in 1, in the middle of the lower part of the abdomen. Three patients showed mild to moderate muscle spasm over the tender area, and 2 showed rebound tenderness.

Data on Seven Cases

Case	1	2	3	4	5	6	7
Age	42	20	28	45	20	48	44
Sex	Female	Female	Female	Female	Male	Male	Male
Duration of symptoms	5 days	2 days	8 days	2 days	3 days	3 days	6 days
Pain at start	Left lower quadrant	Right lower quadrant	Left lower quadrant; right lower quadrant	Lower mid-abdomen	Epigastrium; right lower quadrant	Right lower quadrant	Epigastrium; right lower quadrant
Tenderness	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rigidity	Yes	No	No	No	Yes	Yes	Yes
Nausea	No	No	No	No	Yes	Yes	Yes
Vomiting	No	No	No	No	No	No	Yes
Constipation	No	No	No	Yes	No	No	No
Nutrition	Obese	Good	Good	Obese	Good	Good	Good
Abdominal mass	No	No	Yes	Yes	No	No	No
Temperature, F.	101	99	100	100	100	99	102
White blood cells, per cu. mm.	10,000	8,000	16,000	12,000	10,000	9,000	13,000
Preoperative diagnosis	Perforated sigmoiditis	Acute appendicitis	Diverticulitis	Abscess of abdominal wall	Subacute appendicitis	Subacute appendicitis	Acute appendicitis
Postoperative diagnosis	Torsion of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage

In 1 patient there was found a palpable mass in the left anterior lumbar region, and in another a mass was felt just below the umbilicus. Rectal and vaginal examination elicited tenderness over the affected side in 2 instances.

The white blood cell count was normal for 2 patients; for the others it was elevated, ranging between 10,000 and 16,000 per cubic millimeter. The differential count showed a range of 65 per cent to 80 per cent polymorphonuclear leukocytes.

The preoperative diagnosis was acute or subacute appendicitis for 4 patients, sigmoiditis or diverticulitis for 2 patients and abscess of the abdominal wall for 1 patient. At operation there was a striking simi-

larity in the pathologic picture in all 7 patients; the lesion consisted of an irregular mass mottled yellow, red and blue-black. The mass was firm and indurated, and in 4 patients it was found adherent to the surrounding tissues. The largest of these masses was suspended from the cecum and measured 8 by 2 cm.

The distribution of the lesions was as follows: 2 were associated with the cecum and showed no evidence of torsion; 1 was suspended from the ascending colon and was found twisted on its pedicle; another, similar mass with a twisted pedicle was associated with the transverse colon. In 3 patients the lesion was in the appendices epiploicae arising from the sigmoid flexure; 2 of these were found twisted at operation. In 2 instances serosanguineous fluid was present in the peritoneal cavity. In 5 patients the vermiform appendix was also removed, although in none of these did this structure show gross evidence of pathologic change. In 1 instance an infarcted epiploic appendage arising from the cecum was mistaken at operation for a gangrenous vermiform appendix, for which reason it was removed. Subsequent pathologic examination of the specimen, however, proved it to be a gangrenous epiploic appendage and not an inflamed vermiform appendix. All the 7 patients operated on made an uneventful recovery.

Pathologic examination of the specimens again showed the same picture for all 7 patients. It consisted of irregular, dense yellow, red and blue lobules of adipose tissue separated by thin fibrous connective tissue septums. In 2 instances there was found gross evidence of venous thrombosis of the infarcted appendices epiploicae. In 1 of these patients the appendage, arising from the sigmoid flexure, was found not twisted at the time of operation; another appendage, arising from the transverse colon, showed torsion. The outstanding features in all 7 cases were marked congestion, edema and hemorrhage into the fat and into the connective tissue septum (fig. 2). There was, in addition, a mild inflammatory reaction, in which the exudate consisted for the most part of monocytic cells, polymorphonuclear leukocytes and occasional plasma cells and histiocytes. In 2 patients there was a marked large mononuclear cell infiltration, and in another, with a twisted epiploic appendage, there was an abundant polymorphonuclear cell infiltration suggestive of suppuration.

In general it may be said that there is no train of symptoms or signs characteristic of the disease. Abdominal pain is more or less a constant feature and is described as sharp or colic-like. The location of the pain in the abdomen varies according to the seat of the lesion in the colon. In 4 of the patients the pain was referred to the right lower quadrant, in 2 to the left lower quadrant and in 1 to the middle of the lower part of the abdomen. Another striking symptom in the syndrome of this disease is the disproportion between abdominal tenderness, the duration of symptoms and abdominal rigidity. The abdomen is usually locally

and definitely tender to deep palpation, and the abdominal rigidity is not nearly as marked as one might expect it to be when the possible duration of the complaint and the definite tenderness are considered. Another outstanding symptom of the disease is the marked hyperesthesia of the skin. We have found the same to hold true in cases of infarction involving the larger omentum (Pines and Rabinovitch [13]). The normal leukocytic relation is only moderately disturbed, and the temperature in the uncomplicated case is not elevated.

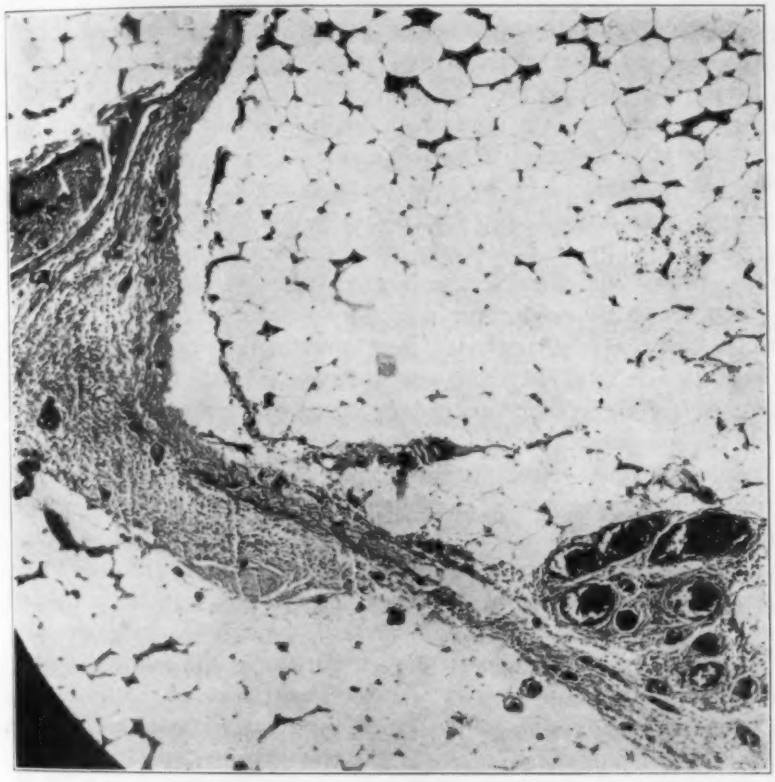

Fig. 2.—Infarct of the epiploic appendage, showing thrombotic occlusion of the blood vessels, hemorrhagic extravasations between the various fat cells and round cell infiltration into the connective tissue septums. × 100.

The diagnosis of torsion and infarction of the appendices epiploicae is usually very difficult, primarily because of the rarity of the condition and the frequency with which other forms of peritoneal irritation are seen. It is especially difficult to make a differential diagnosis from acute appendicitis, diverticulitis, sigmoiditis, mesenteric thrombosis and strangulated internal hernia. Almost all of these lesions present indications

13. Pines, B., and Rabinovitch, J.: Surg., Gynec. & Obst. **71**:80, 1940.

for laparotomy; when the abdomen is open and exploration reveals the true nature of the disease, proper treatment may be instituted.

The cause of torsion of the appendices epiploicae is still obscure and subject to a great deal of controversial discussion. The prevalence of the disease among well nourished and obese persons is significant and at once suggests a causal relation. It is well known that in the obese the appendages tend to be abnormally long, a condition which permits ready twisting because of mechanical reasons (Morestin [14]). Davis expressed the opinion that the long and narrow pedicle of the epiploic appendage is primarily responsible for the production of torsion. We have noted, however, that torsion may occur with equal frequency in the short and wide pedicle. In none of our patients was there a history of sudden exertion or trauma which might have initiated torsion. Such factors as strong abdominal muscle contractions or intestinal peristalsis have been considered by some as precipitating factors, but no definite proof has been offered by the advocates of this hypothesis. It has been suggested by Payr [15] that, since the appendical veins are longer than the corresponding arteries, the former might become twisted around the latter, with the production of infarction because of venous occlusion. Such a condition is particularly prone to occur in cases in which a digestive plethora of the intestinal vascular system exists and in which the distal end of the epiploic appendage is heavier and contains more fat than the proximal portion. It has been shown that a physiologic splanchnic plethora exists during the process of digestion; this is characterized by engorgement of the mesenteric veins. The venous engorgement is most pronounced in the more distal and dependent portion of the appendages. It is easily conceivable that a sudden exertion or trauma during this phase of digestive plethora may stretch and traumatize the delicate venous wall and result in local thrombosis and subsequent infarction. In further support of such an idea is the fact disclosed by one of us (J. R.[16]) in a series of experiments, namely, that a forceful pull on the jugular vein in the rabbit, injuring its endothelial lining, results in the formation of a clot at the site of injury.

In the event of sudden or gradual twisting of the appendices epiploicae or in cases of primary thrombosis of the epiploic vessels aseptic gangrene usually sets in provided no secondary infection supervenes. The gangrenous tissue is subsequently organized, with the formation of a fibrous tissue mass; this mass may become dissociated from the remaining normal tissue and be cast off into the peritoneal cavity as a foreign body. In 1 of the patients cited such a fibrous mass was found almost completely detached from the base of the epiploic appendage.

14. Morestin, H.: Bull. et mém. Soc. anat. de Paris **87**:391, 1912.
15. Payr: Arch. f. klin. Chir. **62**:501, 1902.
16. Rabinovitch, J.: Unpublished data.

Deville, in 1851, found a number of free bodies in the peritoneal cavity, and in 1 instance he noted that an epiploic appendage was about to fall off spontaneously. However, it was not until 1863 that Virchow called attention to the relation of these corpora aliena adiposa, as these bodies have been termed, to the appendices epiploicae. He stated that the increased fat in the appendages of the obese patients is chemically split and calcified and that the increased weight causes obstruction to the circulation, resulting in necrosis and spontaneous sloughing. No mention was made of primary torsion and infarction of the appendices epiploicae as the basic mechanism in the formation of these loose bodies; the latter have been shown to reach a large size (that of a hen's egg) and to contain calcium and occasionally also fibrocartilage. Klingenstein [17] collected from the literature 12 cases of loose intra-abdominal bodies which presumably originated from the appendices epiploicae.

Inflammation of the appendices epiploicae may be superimposed on an area of infarction. It may also result from direct extension of an adjoining inflamed viscus, especially the colon, as in the case of diverticulitis. Primary inflammation of the epiploic appendages is a rare occurrence; several cases have been reported in the literature. A careful scrutiny of the surgical material at the Jewish Hospital failed to reveal any similar cases. We have observed, however, inflammatory reactions in epiploic appendages which have been primarily the seat of infarction.

The various lesions described may be quite innocuous so far as the future health or life of the patient is concerned. They have been shown, however, to produce morbid changes, and in a number of instances they led to death. Thus, Patterson, Klingenstein, Poirier and Baumeister, Hargens and Morsman have reported cases of intestinal obstruction produced by lesions of the appendices epiploicae. In 1 case inflamed appendices epiploicae on either side of the colon became adherent to one another and constricted the bowel at three different levels. The patient died after a cecostomy. Poirier was able to show roentgen evidence of constriction of the terminal portion of the ileum caused by an inflamed epiploic appendage of the sigmoid flexure.

Torsion and inflammation of the appendices epiploicae may go on to ultimate formation of a localized abscess, or generalized diffuse peritonitis may set in, resulting in death, as described by Seelye and in 2 other cases reported in the literature.

17. Klingenstein, P.: Surg., Gynec. & Obst. **38**:376, 1924.

RAPID TISSUE DIAGNOSIS

COMPARISON OF MICROSCOPIC DIAGNOSES OBTAINED FROM TERRY'S RAZOR SECTIONS AND FROM PARAFFIN SECTIONS IN 4,326 BIOPSIES

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Rapid tissue diagnosis during operation has lately fallen into discredit. While many surgeons still are enthusiastic about it, leading pathologists have recently criticized this method as not only unreliable but unnecessary.

According to Simpson,[1] "the Frozen Section Fetish appeals to the surgeon mainly because it adds to the drama in the operating theatre. What better impression can the surgeon make upon visiting practitioners than to toss a specimen to a waiting pathologist and await his return a few minutes later, often out of breath, to give a diagnosis. If the surgeon has faith in his preoperative diagnosis and his gross observations at the time of the operation, such a practice is unnecessary."

Every one will agree with Simpson that rapid tissue diagnosis as an act of surgical showmanship is unworthy of the pathologist as well as of the surgeon. A simple remedy against the abuse of this method is provided by a request by the pathologist for an appointment made the day before the operation and by a reasonable consultation fee.

Simpson opened his encyclic against rapid tissue diagnosis with the citation of an actual observation in which, like a trained seal, the pathologist caught a small bit of breast tissue tossed by the surgeon, rushed to the laboratory, made a hurried microscopic examination, ran back to the operating room and gasped "scirrhous carcinoma." This true story misses the point. If the gross appearance of the "well developed carcinoma was so characteristic that it should have been recognized as such by the surgeon," there was certainly no need for the pathologist to run to his microscope. He should have diagnosed the tumor by gross inspection right in the operating room. After all, the surgeon who consults the pathologist wants an expert diagnosis but cannot dictate the method of diagnosis.

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1. Simpson, W. M.: The Frozen Section Fetish, editorial, Am. J. Clin. Path. **7**:96, 1937.

I am not particularly interested in the question whether rapid tissue diagnosis is necessary. I leave the indications to the surgeon and trust that he will request tissue diagnosis during operation in the interest of the patient and not to glorify himself. As a pathologist, I am much more interested in Simpson's second point, that rapid tissue diagnosis is hazardous and unreliable.

Simpson stated that in a few of the larger clinics certain pathologists have acquired great skill in the preparation and diagnosis of fresh frozen sections, while in smaller laboratories an accurate diagnosis is often impossible. He concluded that any diagnostic method which yields good results only in the hands of a few experts is not adaptable to the average hospital laboratory.

I do not know on what facts Simpson bases his verdict. Certainly there are no statistical data in the literature which allow a comparison between rapid and paraffin sections. Not by generalities, but only by accurate reports on the results of rapid tissue sections can it be determined whether this diagnostic method is justified or, as Simpson concluded, should be abandoned.

The present paper is based on a comparison of microscopic diagnoses obtained from rapid tissue sections and those obtained from permanent paraffin sections in 4,326 biopsies.

TECHNIC

For ten years I have been using Terry's razor sections as the most favored routine method of diagnosing tumor tissue during operation. I follow Terry's [2] original procedure, fastening the specimen with two pins to a cork plate and cutting it with straight biconcave razor. I have given Terry's modification,[3] in which a safety razor blade in a self-made microtome is used, a fair trial, but have returned to his original method.

Its principle is that one need not cut tissue very thin to get histologic detail; relatively thick sections are made with the razor and stained superficially, on one side only, with neutral polychrome methylene blue. The slice of moist tissue, with the stained surface uppermost, is covered with a cover glass and examined with transmitted light from a 100 watt frosted mazda bulb. Since only the upper cell layer is stained and the light is transmitted through the thick, unstained part of the tissue, one has the impression of seeing a perfectly thin microtome section. The nuclei are stained deep blue, while connective tissue and muscle fibers are light rose. Few artefacts are encountered, since freezing, fixing, boiling and dehydrating are completely avoided.

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2. Terry, B. T.: A New and Rapid Method of Examining Tissue Microscopically for Malignancy, J. Lab. & Clin. Med. **13**:550, 1928.

3. Terry, B. T.: An Inexpensive Easily Made Safety Razor Blade Microtome with Technic Especially Useful in the Immediate Microscopic Diagnosis of Tissue, Am. J. Clin. Path. (Tech. Supp.) **7**:69, 1937.

The microscopic picture remains for about six minutes; then the stain fades slowly. Sections may be restained, or, if more material is available, a new section may be cut.

I prefer Terry's supravital technic for the following three reasons:

1. The greatest disadvantage of frozen sections is that the available tissue may be completely used up by the rapid method, and the subsequent employment of other methods is impossible. The preliminary cutting of razor sections does not exclude the later use of paraffin embedding. Even thin razor sections are usually thick enough to be cut in paraffin. Moreover, the staining of sections with polychrome methylene blue does not prevent the subsequent staining of these with

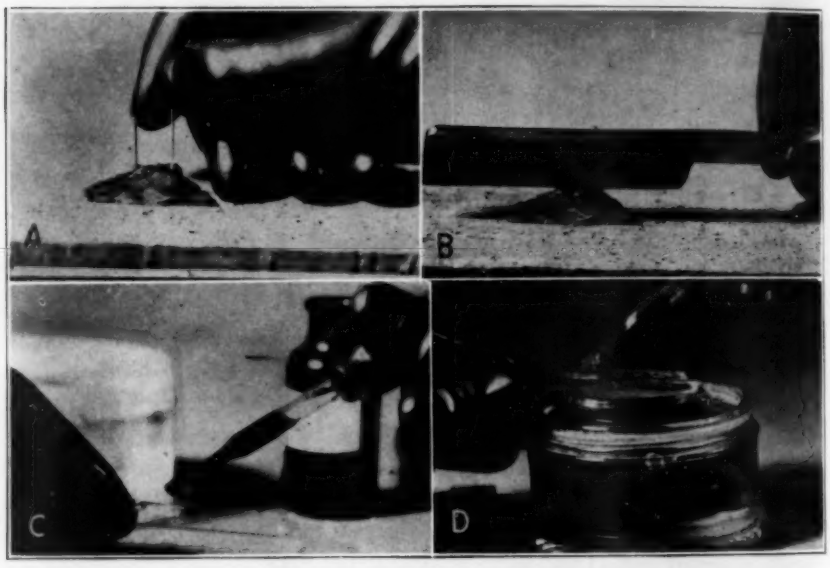

Fig. 1.—Terry's technic. *A*, the biopsy specimen is fastened to a cork board with two pins. *B*, with a biconcave razor a thin slice is cut off. *C*, the section is stained superficially for a few seconds with polychrome methylene blue. *D*, the stain is washed off with water. After covering with a cover glass, the section is examined microscopically by transmitted light.

other stains, for the methylene blue is extracted completely when the tissue is dehydrated.

2. The second reason I prefer Terry's method is that it is so simple that the pathologist is entirely independent of a technician in the preparation of the sections. Examination of the fresh surgical specimen by sight and by touch, selection of the block, the cutting sensation with the razor, the avidity of the tissue for the stain—all these furnish essential and often conclusive information to the pathologist which a ready-made

microscopic frozen section handed him by the technician may never reveal.

3. In rapidity, Terry's method is unsurpassed by any other histologic procedure. In less than one minute the tissue is cut and stained. Therefore Simpson's objection that it is not possible during operation to make several rapid sections from different areas of the biopsy specimen certainly does not hold for Terry's method. Without causing delay for the surgeon, it is easy not only to diagnose the local lesion but to determine accurately the margin that should be given from a benign or malignant tumor and to ascertain whether lymph nodes near the local

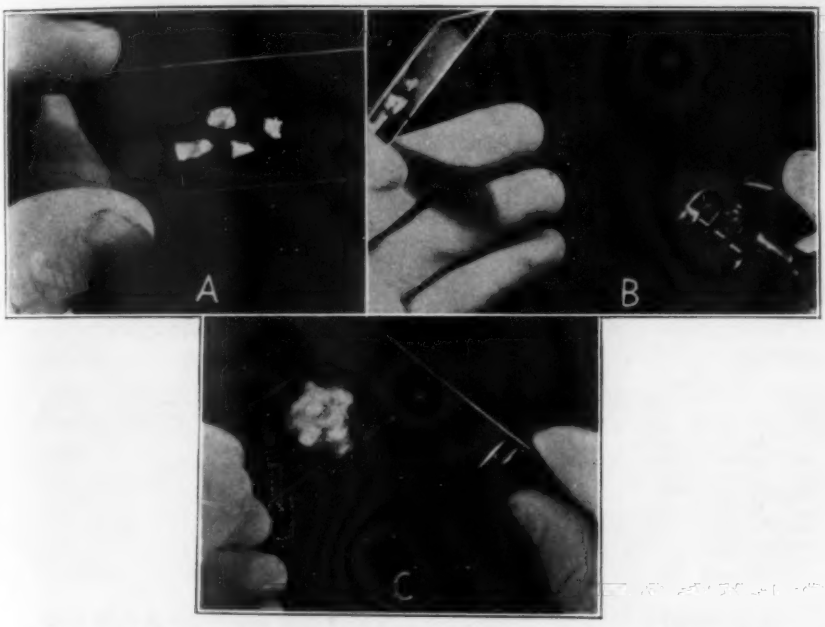

Fig. 2.—Hall's modification of Terry's section. This is used for specimens too small or too friable to fasten on the cork board. *A*, the tissue fragments are placed on a glass slide. *B*, the lower surface of the glass slide is frozen with the ethyl chloride spray. *C*, the upper portion is cut off so that a thin, flat slice remains on the slide. From this point the procedure is continued as shown in figure 1 *C*.

lesion show metastases. Histologic control of the whole operation for tumor is made practicable by this method.

While Terry's original method can be applied successfully to the great majority of biopsy specimens, there is one definite limitation, namely, an extremely small specimen. If it is possible to fasten the piece of tissue with two pins on a cork plate, i. e., if the diameter is at least 5 mm., a good razor section can be obtained as a rule. Curettings or

small fragments of soft tumors of the bladder or rectal polyps are not suitable for this method. For these, Hall's [4] modification has proved of greatest value; it is superior to the use of the freezing microtome. The curettings are placed on a glass slide, and the lower surface of the slide is sprayed with ethyl chloride until the tissue is frozen. With a razor held parallel to the glass slide the upper portion of the tissue is cut away so that a flat piece of tissue about 2 mm. thick remains on the slide. The tissue is allowed to thaw out and is stained exactly like an ordinary Terry section.

TABLE 1.—*Comparison of Microscopic Diagnoses Obtained from Terry's Sections and Paraffin Sections in 4,326 Biopsies*

Year	Cases	Benign	Malignant	Complete Agreement, Percentage	Partial Agreement, Percentage	Doubtful, Percentage	Disagreement, Percentage
1935.....	613	438	175	95.8	2.5	0.6	1.1
1936.....	660	503	166	95.2	2.6	0.9	1.3
1937.....	912	673	239	95.8	1.1	0.6	2.5
1938.....	1,049	760	289	94.6	1.8	0.5	3.1
1939.....	1,083	773	310	95.7	0.8	1.4	2.1
Total....	4,326	3,147	1,179	95.4	1.5	0.8	2.3

TABLE 2.—*Comparison of Microscopic Diagnoses Obtained from Terry's Sections and Paraffin Sections from Different Organs*

Tissue	Cases	Complete Agreement, Percentage	Disagreement, Percentage
Skin.....	815	90.7	4.3
Cervix.....	786	97.6	2.0
Corpus uteri.....	697	98.6	0.7
Lymph node.....	141	90.1	4.3
Mouth.....	284	93.6	2.5

RESULTS

The results in this series of 4,326 biopsies are recorded in table 1. Complete agreement between the histologic diagnoses obtained from razor sections and those obtained from paraffin sections was found in 95.4 per cent of all cases. Malignancy or benignancy was correctly recognized in 96.9 per cent by the rapid method. In 0.8 per cent of all cases the Terry method did not permit a clearcut diagnosis and the surgeon was advised to proceed with his operation on clinical judgment or to await a final diagnosis made from paraffin sections. In 2.3 per cent there was disagreement between the diagnoses obtained from Terry's section and those obtained from paraffin sections.

In table 2 a comparison of histologic diagnosis is made according to different organs. It is evident that noncarcinomatous lesions of

4. Hall, W. E. B.: A Modification of Terry's Method of Rapid Sectioning for Soft Tissues, Arch. Path. **25**:854 (June) 1938.

lymph nodes are the hardest tissues to diagnose by the supravital method. Hodgkin's disease, lymphosarcoma and simple chronic lymphadenitis may look much alike in the razor sections. On the other hand, metastatic carcinoma in lymph nodes is as easily recognized as the primary tumor. The relatively large number of failures in cutaneous biopsies is explained almost entirely by the extremely small size of most of the specimens of skin. Often taken from the face, too sparingly, to avoid disfiguring scars, they are usually too small to be held with two pins on the cork plate. When the size is sufficient, neoplastic tissue is easily recognized in Terry's sections. Inflammatory and metabolic cutaneous lesions may present great diagnostic difficulties to the pathologist also in paraffin sections and often require special staining methods.

The results in diagnosing endometrial scrapings were much better after Hall's modification of Terry's method was adopted.

COMMENT

My results in the diagnosis of supravital sections are in accord with the view held by Wood,[5] that in the vast majority of cases a correct histologic diagnosis can be made in the operating room in a few minutes after removal of the specimen but that it is impossible to make correct diagnoses in 100 per cent of the cases. No general acceptance or condemnation can be made in regard to the usefulness of rapid tissue diagnosis. The success depends on familiarity with a given procedure and on the experience of the microscopist. Other essential factors are: the location of the laboratory near the operating room; the willingness of the pathologist to use the rapid tissue method on every occasion, whether the surgeon requests it or not; the courage of the pathologist to admit his failure when the specimen cannot be diagnosed by supravital technic, and the understanding of the surgeon that rapid tissue diagnosis will fail in 3 per cent of all cases.

From a ten year experience I am convinced that surgeons who thoroughly understand the limitations of the method appreciate the possibility of having a correct microscopic diagnosis in all but a few cases during operation. Even if the surgeon is not interested in rapid tissue diagnosis, I cannot see how the pathologist in his daily routine can get along without it. For years I have made Terry's razor sections from every tumor specimen which comes to my laboratory, whether the surgeon requests it or not. The gross diagnosis of tumor tissue is stressed more and more (Ewing[6]). There is no better way to gain experience in the gross diagnosis of tumors than by razor sections.

5. Wood, F. C.: The Diagnosis of Cancer, J. A. M. A. **95**:1141 (Oct. 18) 1930.

6. Ewing, J.: Causation, Diagnosis and Treatment of Cancer, Baltimore, Williams & Wilkins Company, 1931, p. 43.

Using this method, the pathologist can associate in his mind the gross and the microscopic picture within a few minutes, while the preparation of paraffin sections brings a delay of several days. The selection of suitable blocks for paraffin embedding is also much facilitated by first obtaining Terry sections from different portions of a specimen.

The microscopic examination of fresh tissue, which played a large part in the earlier days of histopathology, seems at present a lost art. Henke,[7] in his "Guide to Tumor Diagnosis," pointed out that the microscopic diagnosis of fresh tissue is neglected without reason by those who rely on the modern embedding and staining methods and that in some cases only the examination of fresh tissue enables one to recognize the finer cell structures as they exist in the living stage. To do justice to the patient, no examination of tumor tissue can be regarded as complete unless all three diagnostic methods are employed—the inspection and palpation of the gross specimen, the microscopic examination of supravital preparations and, finally, the leisurely study of paraffin sections.

No experienced pathologist will deny that rapid tissue diagnosis has its limitations, but the art of its employment lies in a thorough understanding of these limitations. There are, on the other hand, such great advantages in the use of rapid tissue diagnosis that it should be used in all biopsies in addition to paraffin sections.

Terry's supravital technic is as simple, as fast and as economical as a bacteriologic smear and is, in my opinion, an indispensable tool of the modern laboratory, large or small.

CONCLUSIONS

In the vast majority of cases of tumor a correct histologic diagnosis can be made during operation within a few minutes after removal of the specimen. In 4,326 biopsies, the microscopic diagnoses obtained from rapid tissue sections and paraffin sections were in complete agreement in 95.4 per cent of all cases.

Terry's supravital technic is superior to the frozen section method. It should be adopted by surgical laboratories as the standard method of rapid tissue diagnosis.

7. Henke, F.: Mikroskopische Geschwulstdiagnostik, Jena, Gustav Fischer. 1906, p. 12.

SPINAL ANESTHESIA AND SURGICAL SHOCK

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A marked fall in blood pressure during an operation with general or local anesthesia is usually accepted as an indication of severe hemorrhage, surgical shock or both. This has led many surgeons to believe that the fall in blood pressure which regularly accompanies the induction of spinal anesthesia has equally grave significance. On the basis of the same kind of reasoning, various technics have been introduced either to prevent the fall in blood pressure or to raise the pressure after it has reached what is considered a dangerously low level, and it has been argued that spinal anesthesia is contraindicated in the presence of the hypotension secondary to traumatic shock, hemorrhage and peritonitis.

On the other hand, in a previous report one of us (Koster [1]) concluded, on the basis of 3,500 experiences with spinal anesthesia, that the fall in blood pressure, no matter how marked, is not of great significance and also that hypotension per se is no contraindication to the use of this anesthesia. Since then, over 10,000 additional experiences have confirmed this view and have led us to believe that there is a marked difference between the circulatory status of patients under spinal anesthesia and that of patients in surgical shock.

Recent studies [2] have shown that in cases of "surgical shock" not accompanied with hemorrhage the fall in blood pressure is preceded by marked hemoconcentration. In fact, it has been maintained that hemoconcentration, as evidenced by a rise in the red cell count, the hemoglobin concentration or the specific gravity of the whole blood, is a better index of the presence and severity of "shock" than is a fall in blood pressure.

To determine whether the fall in blood pressure which occurs during spinal anesthesia is similar to that associated with surgical shock, we studied the blood pressure and the concentration of hemoglobin in the blood before, during and after spinal anesthesia.

From the Richard Morton Koster Research Laboratory.

1. Koster, H.: Am. J. Surg. **5**:554, 1928.

2. (*a*) Blalock, A.: Internat. Clin. **1**:144, 1933. (*b*) Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940. (*c*) Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

Seven patients were anesthetized by injecting 150 mg. of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid into the subarachnoid space between the second and third lumbar vertebrae [1] and were placed in the Trendelenburg position (about 8 to 10 degrees). Systolic and diastolic pressures were determined by the auscultatory method at intervals of about ten minutes throughout the duration of the anesthesia and at somewhat longer intervals thereafter. The concentration of hemoglobin was determined on finger blood obtained from a freely flowing puncture wound before the induction of anesthesia,

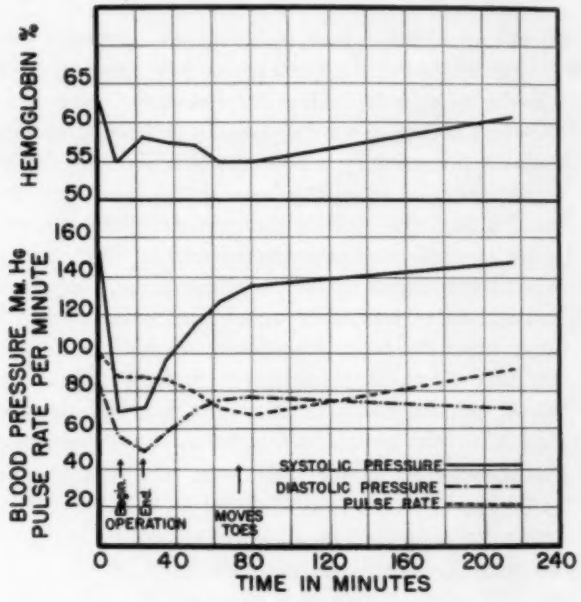

Chart 1.—Data in a typical case.

at intervals of approximately ten minutes during the anesthesia and approximately two hours after the termination of the anesthesia.

The hemoglobin determinations were done according to a modification of the method of Sanford, Sheard and Osterberg.[3] Blood (0.02 cc.) was placed in 10 cc. of 0.1 per cent sodium carbonate solution. The intensity of the color was determined in a photoelectric colorimeter, with a no. 978 Corning filter. A fragment of colorless fibrin was occasionally seen in the solution, but this could be easily removed by means of a capillary pipet.

The results are presented in table 1. The data on a typical case are shown graphically in chart 1.

3. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: Am. J. Clin. Path. 3:412, 1933.

TABLE 1.—*Effect of Spinal Anesthesia on Hemoglobin*

Operative Procedure	Initial Blood Pressure, Mm. Hg		Lowest Blood Pressure, Mm. Hg		Initial Pulse Rate	Slowest Pulse Rate	Initial Hemoglobin, per Cent	Lowest Hemoglobin, per Cent	Maximum Fall				Maximum Fall, per Cent			
									Blood Pressure, Mm. Hg				Blood Pressure			
	Systolic	Diastolic	Systolic	Diastolic					Systolic	Diastolic	Pulse Rate	Hemoglobin	Systolic	Diastolic	Pulse Rate	Hemoglobin
1. Incision and drainage; removal of metatarsal bone....	104	76	80	52	116	92	80.3	71.1	24	24	24	9.2	23	32	21	11
2. Hernioplasty..	154	83	60	42	101	80	62.4	55.0	94	41	21	7.4	61	50	21	12
3. Supracervical hysterectomy; appendectomy; bilateral salpingo-oophorectomy	198	108	98	56	120	52	100	90.3	100	52	68	9.7	50	48	56	10
4. Hernioplasty..	132	90	102	44	102	92	101.7	100.3	30	46	10	1.4	23	51	10	1
5. Orchidopexy...	136	80	90	60	80	56	96.5	91.5	46	20	36	5.0	34	25	45	5
6. Open reduction of fracture of neck of femur	166	100	0	0	94	68	80.0	67.0	166	100	26	13.0	100	100	28	16
7. Hernioplasty..	140	90	70	40	104	48	103.5	96.5	70	50	56	7.0	50	56	54	7
												Average	49	52	34	9

In 6 of the 7 cases the results are entirely comparable in that they show an immediate fall in the level of hemoglobin of 1 per cent to 16 per cent accompanying the fall in blood pressure and then a gradual return of both the concentration of hemoglobin and the blood pressure toward the initial level. In none of these 6 cases at any time during the observations did the value for hemoglobin reach the initial level. In the seventh case (chart 2), in which the initial value for hemoglobin was 104 per cent, there was a drop to 97 per cent at the end of six minutes. After this the concentration of hemoglobin rose gradually, until at thirty-six minutes it was 104 per cent. It reached 106 per cent

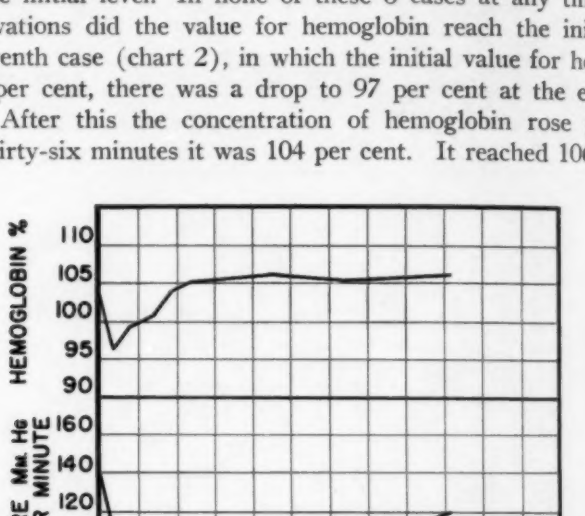

Chart 2.—Data in the case in which the content of hemoglobin rose beyond the original level.

at eighty-nine minutes and remained there at the end of one hundred and eighty-three minutes.

It is clear, then, that in the first 6 cases the values for hemoglobin indicated hemodilution rather than hemoconcentration. In the seventh case there was an initial hemodilution of about 7 per cent. The final hemoconcentration, of 2 per cent, is probably not significant.

The fall in hemoglobin may be due to pooling of the red cells somewhere off the main circulatory pathway (liver? spleen?) or to a shift of fluid into the circulatory system. To check this point, samples of blood were removed from an arm vein of each of 10 patients before the induction of spinal anesthesia, at ten minute intervals during anesthesia

and two hours after the disappearance of anesthesia. The specific gravity of the serum was determined by the falling drop method.[4]

The results of these determinations paralleled those of the hemoglobin determinations. There was either a slight initial fall, with gradual recovery, or no significant change.

Altogether our data indicate that the fall in blood pressure occurring with spinal anesthesia is neither preceded by nor accompanied with hemoconcentration but is, on the other hand, often accompanied with slight hemodilution, and this is evidently due to the addition of protein-free fluid to the circulating blood.

In cases of surgical shock, cardiac output falls before and after the fall in blood pressure.[2a] For spinal anesthesia the data available are not so complete or so satisfactory, but it is probable that the fall in blood pressure is generally accompanied with some fall in cardiac output.[5]

The data just given, however, suggest that the clinical significance of the diminished cardiac output in cases of surgical shock and in the presence of spinal anesthesia may not be strictly comparable. The supposed similarity in the clinical status of the patient in surgical "shock" and the patient under spinal anesthesia, therefore, deserves closer examination. A detailed comparison is given in table 2.

It is seen that of the seventeen characteristics compared, spinal anesthesia and surgical shock show complete similarity in only two, namely, the appearance of the face and the vomiting. There is partial similarity in moisture of the skin, thirst, venous pressure and mental attitude. The fall in blood pressure which has usually been considered the cardinal point of similarity between surgical shock and spinal anesthesia actually has quite different characteristics in each. In the presence of shock the fall occurs late, after compensatory vasoconstriction no longer is effectual in maintaining the normal level of blood pressure. By this time hemoconcentration is already marked. In the presence of spinal anesthesia the blood pressure falls early, and hemoconcentration does not occur. In the remaining eight characteristics analyzed in the table there is a clearcut difference between surgical shock and spinal anesthesia.

It is apparent, then, that the clinical status of a patient in surgical shock is almost entirely different from that of one under spinal anesthesia. Valid indications and contraindications for the use of spinal anesthesia must therefore be based either on an analysis of its physiologic effect or on clinical experience with its use. Reasoning based on the

4. Kagan, B. M.: J. Clin. Investigation **17**:369, 1938.

5. (*a*) Goldfarb, W.; Provisor, B., and Koster, H.: Circulation During Spinal Anesthesia, Arch. Surg. **39**:429 (Sept.) 1939. (*b*) Schubert, O. O.: Acta chir. Scandinav. (supp. 43) **78**:1, 1936.

supposed analogy between the clinical status of patients in surgical shock and that of patients under spinal anesthesia is necessarily unsound.

SUMMARY

In 7 patients the blood pressure, pulse rate and concentration of hemoglobin were followed before, during and after spinal anesthesia, and in 10 patients the blood pressure, pulse rate and specific gravity of the serum were similarly studied.

TABLE 2.—*Comparative Analysis of Spinal Anesthesia and Surgical Shock*

	Surgical Shock	Spinal Anesthesia
Appearance of face	White, pale, grayish or slightly cyanotic	Same
Vomiting	Present	Present
Perspiration	Profuse	Moderate; present only in the unanesthetized areas *
Thirst	Marked	Slight in occasional instances*
Venous pressure	Low	Slightly reduced [5a]
Mental attitude	Restlessness and anxiety merging into listlessness, apathy and unconsciousness	Not characteristic; ranges in different patients from euphoria to attitudes similar to those in surgical shock *
Blood pressure	Normal until late and then falls	Falls early
Body temperature	Subnormal	Unchanged
Pulse	Rapid and feeble	Slowed and feeble
Temperature of skin	Cold all over	Elevated in anesthetized areas †
Blood pressure response to vasoconstrictor drugs	Slight and transient once blood pressure has fallen	Immediate rise; sustained after certain drugs
Oxygen consumption	Diminished	Unchanged ? [5a,b]
Leukocytosis	Present	Absent *
Respiration	Rapid	Slow *
Blood volume	Diminished	Unchanged [5a]
Hemoglobin concentration	Increased	Slightly diminished (table 1)
Prognosis	Grave if untreated	Good if untreated *

* Unpublished data.
† Scott, W. J. M., and Morton, J. J.: Sympathetic Activity in Certain Diseases, Especially Those of Peripheral Circulation, Arch. Int. Med. **48**: 1065 (Dec.) 1931.

The data indicate that the value for hemoglobin and the specific gravity of the serum fall slightly with the onset of the anesthesia and return gradually to their initial level.

The absence of hemoconcentration suggested a reexamination of the supposed similarity of the clinical status of patients in surgical shock to that of patients under spinal anesthesia.

The characteristics of the clinical status of patients in the two states are fundamentally different.

Reasoning concerning indications or contraindications for spinal anesthesia, based on the supposed analogy between its effects and the state of "surgical shock," is not valid.